Assessment of Anticoagulation Knowledge and Adherence in Patients with Atrial Fibrillation

by

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STATEMENT OF ETHICAL CONDUCT

The research associated with this thesis abides by the Australian codes on human and animal experimentation, the guidelines by the Australian National Ethics and Institutional Biosafety Committees of the University. All research involving patients with atrial fibrillation and healthcare professionals was conducted under the approval of the Tasmanian Human Research Ethics Committee (Approval numbers H0015153, H0015395 and H0015972).

Kehinde O Obamiro

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STATEMENT OF CO-AUTHORSHIP

Given that this thesis is presented as a sequences of papers, either published, in press or submitted, statement of co-authorship are provided for each chapter. Due to this thesis format some repetition is expected.

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PUBLICATIONS

All publications listed resulted from work described in this thesis.

Peer-reviewed Journal Publications

1. Kehinde O. Obamiro, Leanne Chalmers, Luke R. Bereznicki. A Summary of the Literature Evaluating Adherence and Persistence with Oral Anticoagulants in Atrial Fibrillation. Am J Cardiovasc Drugs. 2016;16(5):349-63.

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2. Kehinde O. Obamiro, Chanelle A. Rolls, Leanne Chalmers, Luke R. Bereznicki. The relationship between anticoagulation knowledge, health literacy and medication adherence in patients with atrial fibrillation. Australasian Pharmaceutical Science Association (APSA) Annual Conference 2016. Sydney, December 2 - 5, 2016.

3. Kehinde O. Obamiro, Leanne Chalmers, Kenneth Lee, Bonnie J. Bereznicki, Luke R. Bereznicki. Gaps in oral anticoagulant knowledge. Australasian Pharmaceutical Science Association (APSA) Annual Conference 2017. Brisbane, December 5 - 8, 2017.

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ABBREVIATIONS

Acronym	Definition
AF	Atrial fibrillation
OAC	Oral anticoagulant
VKA	Vitamin K antagonist
DOAC	Direct acting oral anticoagulant
HCP	Healthcare practitioner
AKT	Anticoagulation Knowledge Tool
STOFLHA	Short Test of Functional Health Literacy in Adults
MMAS-8	8-item Morisky Medication Adherence Scale
AFEQT	Atrial Fibrillation Effect on Quality of Life
PACT-Q	Perception of Anticoagulant Treatment Questionnaire
CIO	Cancer Information Overload

ABSTRACT

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, and is responsible for 20-30% of all strokes. AF-related strokes are more severe, and result in longer hospital stays and higher mortality compared to non-AF-related strokes. In Australia, the prevalence of AF is 5.35% in individuals aged 55 years and older, and it is associated with a cost of at least AUD$1.25 billion per year, resulting largely from the incidence of stroke, heart failure and premature mortality.

Oral anticoagulant (OAC) therapy is highly effective for stroke prevention in patients with AF; however, it is also associated with the potential risk of bleeding. Evidence from clinical trials demonstrates that OAC therapy reduces the risk of stroke by 64% to 70%, and is associated with a rate of major bleeding events of up to 3.6% per year. For optimal benefit to be derived from OAC therapy, patients are required to adhere to the prescribed regimen and have sufficient knowledge regarding their medication. Various studies have demonstrated associations between suboptimal adherence and inadequate knowledge regarding OAC therapy with poor treatment outcomes. Suboptimal adherence to OAC therapy has been associated with increased risks of both bleeding and embolic events, while inadequate knowledge has been associated with poor anticoagulation control, which in turn is associated with poorer clinical outcomes. This suggests that OAC knowledge and adherence are important concepts to be considered in high quality management of patients with AF.

Assessment of medication knowledge in routine clinical practice requires the use of validated psychometric instruments. The majority of studies conducted in patients with AF have utilised instruments of unknown validity to evaluate OAC knowledge. This makes it difficult to ascertain whether OAC knowledge has been appropriately assessed. In the last decade, the Anticoagulant Knowledge Assessment (AKA) by Briggs *et al* and the Oral Anticoagulant Knowledge test (OAK) by Zeolla *et al* were developed and validated to assess OAC knowledge. However, both the OAK and AKA are only able to assess knowledge related to the use of vitamin K antagonists (VKAs), and are not applicable to the direct-acting oral anticoagulants (DOACs). An instrument that caters for both patients taking VKAs and DOACs would be useful in clinical practice to identify knowledge deficit in patients with AF, and to guide subsequent educational intervention.

Additionally, there is a lack of contemporary data regarding OAC knowledge level and the rate of non-adherence to OAC therapy in Australia, and their relationship with patient-related factors. Contemporary data are necessary to assess the adequacy of OAC knowledge in the population, and address any deficiencies or misconceptions. Furthermore, contemporary data are needed to identify the barriers to OAC adherence, and identify relevant predictors of non-adherence in the population. Studies related to OAC knowledge and adherence that have been conducted in Australia to date have focused primarily on participants taking VKAs (warfarin). Given the increased rate of prescription of DOACs, as well as switching of patients previously taking warfarin to DOACs, recent data on OAC therapy would be useful in evaluating the impact of DOAC prescribing on patients' knowledge level and adherence to therapy. Accordingly, the development of this thesis was guided by the Capability, Opportunity and Motivation Model of Behaviour (COM-B), which hypothesises that interaction between three components, Capability, Opportunity and Motivation (COM), influence the performance of Behaviour (B). Factors related to each of the three components were explored as they influence OAC adherence.

Therefore, the overall objective of this research was to fill these gaps by developing an instrument that caters for all OACs, and assessing OAC knowledge and adherence in patients with AF.

The specific aims were:

- To develop and validate a new OAC knowledge instrument that caters for both VKAs (warfarin) and the DOACs.
- To use this instrument, the Anticoagulation Knowledge Tool (AKT), to investigate the relationships between OAC knowledge, adherence and health literacy in patients with AF.
- To determine the level of OAC knowledge in patients with AF taking OAC therapy (either warfarin or a DOAC), identify any domains where significant knowledge gaps exist, and assess the association between patient-related factors and OAC knowledge.
- To estimate the proportion of patients who are non-adherent to OAC and identify predictors of adherence, and to determine if patient-related factors vary across levels of adherence in patients with AF.

Due to the absence of a suitable instrument to assess OAC knowledge, we began this research by conducting a comprehensive review of the literature on anticoagulation knowledge, from which a draft instrument was developed. Ten anticoagulation experts were contacted to provide feedback on the draft instrument using a Likert scale, after which the content validity index for the instrument was calculated. For construct validity, three groups of participants comprising of 44 pharmacists, 50 patients and 50 members of the general public were tested using the instrument developed, and the results of these three cohorts were compared. Reliability analyses were conducted to determine if included items were measuring the same general construct, and if the instrument could provide consistent results. A subgroup of participants in the patient and pharmacist groups were re-tested approximately 2–3 months after the initial testing to assess test-

retest reliability using Pearson's correlation coefficient, while internal consistency reliability was assessed by calculating a Cronbach's α value for the three groups. The final 28-item instrument, called the AKT, has a scale content validity index of 0.92, supporting content validity. The pharmacist group's mean score (94%) was significantly higher than that of the patient group (62%), and the patient group scored significantly higher than the general public group (20%) ($p < 0.001$), supporting construct validity. Internal consistency reliability was acceptable with a Cronbach's α value of >0.7 across the three groups, and test-retest reliability was confirmed with a Pearson's correlation coefficient of 0.72 and 0.78 for the pharmacist and patient groups, respectively.

After the development of the AKT, the instrument was piloted in a study involving 48 patients designed to investigate the relationships between OAC knowledge, adherence and health literacy in patients with AF. Participants were recruited from general practices for a face-to-face interview using the AKT to assess OAC knowledge; the Morisky Medication Adherence Scale (MMAS-8) to assess adherence; and the Short Test of Functional Health Literacy in Adults (s-TOFHLA) to assess health literacy. Participants had mean scores of 61.6 ± 15.8, 7.2 ± 1.1 and 24.7 ± 9.5 for the AKT, MMAS-8 and s-TOFHLA, respectively. Significant correlations were observed between OAC knowledge and health literacy with medication adherence (0.37, $p = 0.009$ and 0.30, $p = 0.042$, respectively), and between OAC knowledge and health literacy (0.31, $p = 0.033$). Participants with inadequate health literacy had a significantly lower mean knowledge score than those with adequate health literacy (55.8 ± 15.9 versus 66.1 ± 14.4, $p = 0.022$). In addition, participants who reported adequate adherence to OAC therapy had significantly higher knowledge scores than those who did not (67.5 ± 13.3 versus 56.1 ± 16.2, $p = 0.011$).

After confirming the usability and adequacy of the AKT, the next phase of this research focused on assessing OAC knowledge and adherence in patients with AF in a nationally representative

sample of patients with AF. The study was designed as an online survey to improve reachability and ensure better representation. Survey components used included the AKT, the Perception of Anticoagulant Treatment Questionnaires (assessing treatment expectations, convenience and satisfaction), a modified Cancer Information Overload scale to assess perception of information overload, and the MMAS-8 to assess OAC adherence. Although participants taking warfarin had a higher knowledge score compared to those taking DOACs (n = 386, 73.4 ± 13.2 versus 65.7 ± 13.7, p <0.001), knowledge gaps were generally observed in key areas of self-management including the following: missing a dose, drug interactions and recognising bleeding as an important side effect. Patient-related factors including age in years (p = 0.009) and perception of information overload (p <.001) were significant predictors of knowledge.

To estimate the proportion of patients who were non-adherent to OAC therapy, and identify factors associated with adherence in the population, a secondary analysis of the data was conducted. Non-adherence to OAC therapy was common, as only 54.9% of participants reported a high adherence to OAC. Participants aged ≤65 years were less likely to have high adherence compared to older participants (OR, 0.54; 95% CI, 0.33 – 0.88; p = 0.013), while females were more likely to be highly adherent compared to males (OR, 1.69; 95% CI, 1.08 – 2.64; p = 0.023). Moreover, the result of the secondary analysis showed that treatment satisfaction (p <0.001) and perception of information overload (p <0.001) varied across adherence levels.

Mapping the results from this research to the COM-B framework suggests that each of the components could be explored to improve OAC adherence. Improving knowledge and health literacy levels may increase patients' psychological capability to engage in the necessary thought process that would encourage adherence to OACs. Potentially, healthcare practitioners could use the results of this research to help shape patients' perception and beliefs concerning OAC therapy

to improve motivation to adhere to therapy. Additionally, routine follow-up of both patients taking warfarin and DOACs would possibly improve healthcare practitioner-patient communication, thereby, providing physical opportunity that facilitates appropriate medication-taking behaviour.

This body of work resulted in the development and validation of a novel psychometric instrument for the assessment of OAC knowledge that caters for patients taking either VKAs or DOACs. This research has also identified that significant positive associations between OAC knowledge, adherence and health literacy exist among patients with AF. This suggests that these three components are interrelated, and addressing any of the individual components could help to address one or more of the other two components. Therefore, future interventions to improve knowledge and adherence should also consider the level of health literacy in participants.

Furthermore, this body of work has identified that significant knowledge gaps exist in patients taking OACs, and these deficiencies appeared to be greater in patients taking DOACs. Knowledge assessment should be integrated within counselling sessions to help identify and resolve knowledge deficits in all patients with AF. Finally, this research has demonstrated that self-reported non-adherence to OAC is common among patients with AF. A focus on supporting people who are at higher risk of non-adherence will be helpful in maximising the benefits of OAC therapy. Future studies are required to investigate the best strategies for improving OAC knowledge and adherence in the population.

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CHAPTER ONE
1.0 Thesis background

1.1 Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, and is a significant independent risk factor for ischemic stroke (1). AF is characterised by uncoordinated electrical activation of the atria and an irregular ventricular response leading to hemodynamic compromise (2). While the atria fibrillate, blood pools in the atria, which increases the likelihood of a clot forming in the atrial appendage, thereby increasing the risk of embolic stroke (2). AF is predicted by a p-wave of prolonged duration and abnormal morphology on the electrocardiogram (3), and is often associated with structural heart disease; however, it may be present in patients without any detectable heart disease (4). Patients with AF have a five-fold increase in their stroke risk (5); AF-related strokes are more severe and more likely to result in death than strokes in patients without AF (6, 7). In 2014, the prevalence of AF in Australia was estimated to be 5.35% in individuals aged 55 years and older, and this is expected to increase to 6.35% by the year 2034 (8).

Globally, AF is associated with increased hospitalisation, healthcare costs and premature mortality (9). In the UK, the incidence of AF-related hospitalisation increased from 800,000 to over 2,000,000 in less than 15 years (10). In the US, over 750,000 AF-related hospitalisations occur each year, and the deaths of an estimated 130,000 patients are AF-related (11). Similarly, in Europe, 2.5 million hospitalisation per year are reported to be due to AF (12). In Australia, an estimated 45,000 hospitalisations due to AF occur each year (8).

AF imposes a significant economic burden (13-16). In the UK, AF accounts for 1% of the National Health Service budget; this is estimated to be £1 billion (AU $1.7 billion) (13). Data from the US

showed that AF costs the economy $6 billion (AU $7.7 billion) annually, and the medical costs of patients with AF are $9000 (AU $11,600) higher than those who do not have AF (15). In Europe, the cost of AF to the economy has been estimated to be €3,000 (AU $4,500) annually per patient, with the total economic burden estimated at €13.5 billion (AU $20.4 billion) (14). In Australia, the estimated cost of AF to the economy is at least AU $1.25 billion per year, with 64% of this cost associated with the incidence of stroke, heart failure or premature mortality (16).

Anticoagulant medications are used in the management of thromboembolic disorders that can occur due to a number of medical conditions, including AF (17). Oral anticoagulant (OAC) therapy is highly effective for stroke prevention in patients with AF, and anticoagulants are broadly classified into two groups; the vitamin K antagonists (VKAs) and the direct oral anticoagulants (DOACs) (18). The VKAs competitively inhibit vitamin K epoxide reductase complex, an essential enzyme for activating vitamin K in the body (19). Through this mechanism, VKAs interfere with the carboxylation of all vitamin-K dependent coagulation factors, resulting in lower plasma levels of multiple procoagulant (factors II, VII, IX, X) and antithrombotic factors (Proteins C and S) (19). The DOACs, however, bind at the active site of coagulation enzymes and inhibit a single protease (20). Specifically, apixaban and rivaroxaban are factor Xa inhibitors, and they act by decreasing the amount of thrombin generated, while the direct thrombin inhibitor (dabigatran) inhibits thrombin after it is already formed (21). The mechanisms of action of the DOACs have been modelled using the classical coagulation model, and more recently, using the cell-based model of coagulation (19). In the classical model, the process of thrombin generation is illustrated as a continuous cascade and interactions between cells and coagulation factor are limited; as such, the points of inhibition by DOACs are easily represented (19). The cell-based model of coagulation, however, is more complex and models the process of thrombin generation as occurring on cell surfaces in overlapping phases (19). In the cell-based model, factor Xa inhibitors exert their

anticoagulant effect during the initiation and propagation phases, while thrombin inhibitors exert their effect during the amplification phase (figure 1) (19, 21).

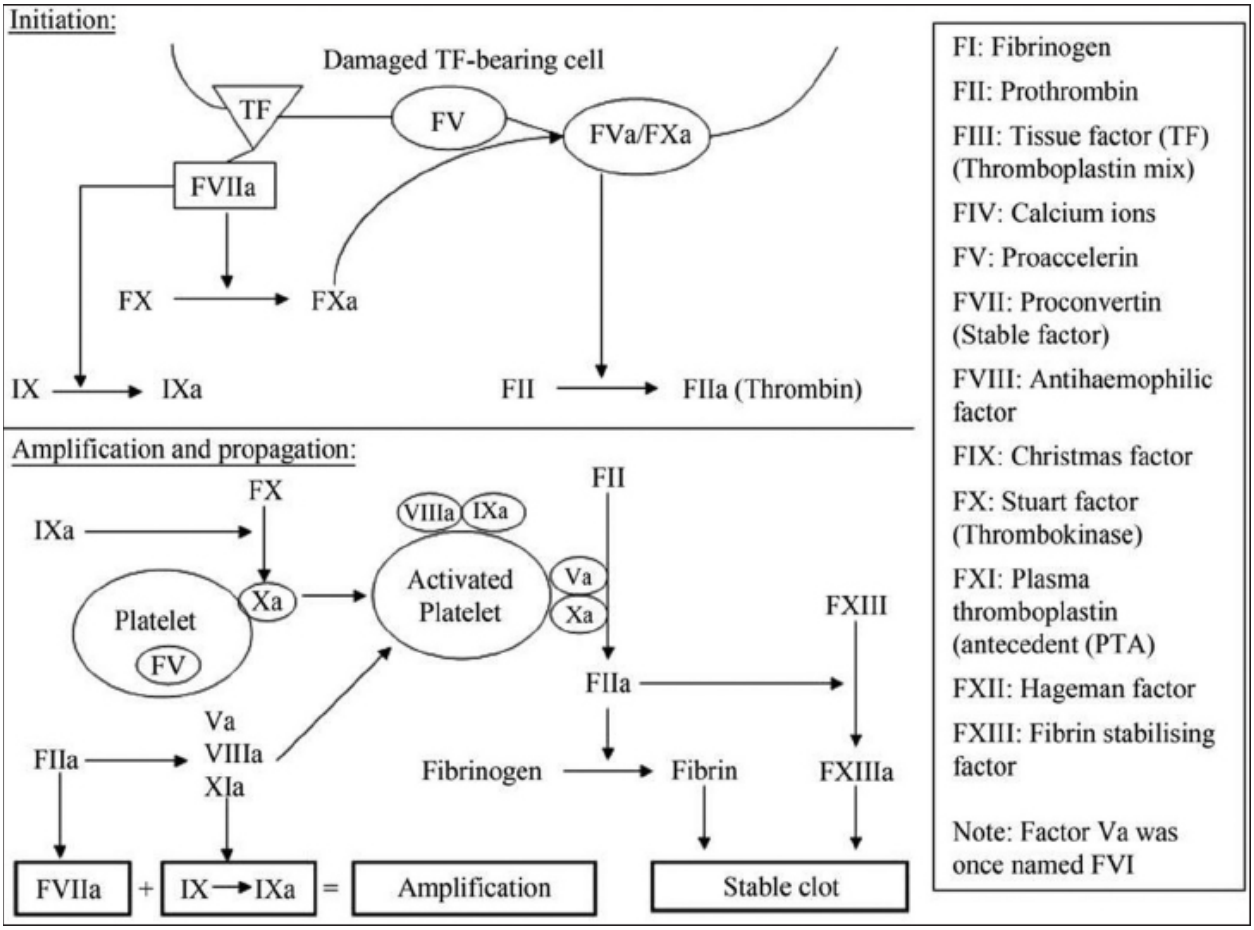

Figure 1: An overview of the cell-based model of coagulation

Adapted from Curry and Pierce, 2007 (22).

Warfarin has been in use for more than 50 years and requires intensive coagulation monitoring; there is wide variation in dose-response relationships, and multiple drug-food and drug-drug interactions (23). The DOACs (dabigatran, apixaban, rivaroxaban) have only been recently introduced into clinical practice, and are expected to overcome the limitations of warfarin therapy (Table 1) (23). Key differences exist in the clinical management of patients taking VKAs and

DOACs. DOACs provide major advantages over VKAs, including fewer drugs interactions, a rapid onset and offset of action, predictable pharmacokinetic profiles, and no requirement for routine coagulation monitoring (18). Although the absence of routine coagulation monitoring makes DOACs more convenient to use, this could also be a potential hazard due to the lack of opportunities for assess the degree of anticoagulation in an individual, adherence assessment and knowledge reinforcement (24). Warfarin is associated with a 60-70% relative reduction in stroke risk and a reduction in mortality of 26% (25), while the DOACs are either comparable or superior to warfarin for stroke prevention in AF and are associated with an approximate 10% reduction in all-cause mortality (26). Despite the documented efficacy of these therapeutic strategies in clinical trials, optimal treatment outcomes in the real world setting involve safe and appropriate use of medication (18).

Patients with optimum knowledge and adherence to OAC therapy are more likely to achieve optimal treatment outcomes, compared to those who do not (27). This has been highlighted by the result of various studies investigating the relationship between adherence levels and OAC knowledge with treatment outcomes. For example, Yao *et al* reported an increased risk of stroke in patients with AF, who were not taking OAC for six months or more (28). Similarly, Tang *et al* reported patients' knowledge of OAC therapy to be an important determinant of anticoagulation control (29).

Table 1. Pharmacokinetic characteristics of the DOACs compared with warfarin		
	Warfarin	**DOACs (dabigatran, apixaban, rivaroxaban)**
Pharmacokinetics	Unpredictable	Predictable
Onset of action	Slow onset	Rapid onset of action
Monitoring requirement	Routine INR	No requirement
Food interaction	Significant	No significant interaction
T_{max} (hours)	72-120	Dabigatran 2-3; apixaban 1-3; rivaroxaban 2-4
$T_{1/2}$ (hours)	20-60	Dabigatran 12-17; apixaban 8-15; rivaroxaban 5-9
INR International Normalised Ratio, T_{max} time to maximum plasma concentration, $T_{1/2}$ half-life		

Adapted from Akinboboye, 2015 (23). Reproduced in accordance with the Creative Commons Attribution Non Commercial license.

1.2 Rationale

Knowledge of therapy (29) and medication adherence (30) are two key factors that can affect the treatment outcome of patients with AF. Evidence suggests that increased knowledge of a condition and medication leads to improved patient adherence to medication and lifestyle changes (31). Medication non-adherence is of significant concern in the management of patients with AF, as it has been associated with an increase in the incidence of stroke, bleeding episodes, hospitalisation and mortality (28). This is because plasma levels of oral anticoagulants need to be maintained at a therapeutic level in order for patients to derive optimal benefit from OACs (18).

Studies conducted to date have investigated anticoagulation knowledge in diverse populations. However, many of these studies have been limited by the use of non-validated instruments. In

cases where a validated instrument was used, the instrument did not cater for the recently introduced DOACs. Given the increased uptake of the DOACs in clinical practice, especially the growing tendency to switch patients taking warfarin to one of the DOACs (32), it was necessary to develop and validate an instrument that is able to assess oral anticoagulation knowledge and can cater for all currently prescribed OACs. This thesis aimed to address this need by developing an instrument that would be useful in assessing anticoagulation knowledge in routine clinical practice, as well as in research, irrespective of the anticoagulants patients are taking.

In Australia, contemporary data are needed to help understand knowledge and adherence gaps in patients with AF, and to identify specific areas where patients require additional support. In addition, the relationship between patient-related factors with OAC knowledge and adherence is yet to be extensively studied. This would be useful in identifying modifiable factors that could be targeted to improve OAC knowledge and adherence in patients with AF.

Overall, while the importance of anticoagulation knowledge and medication adherence are widely recognised in the literature, there is a need for a knowledge assessment instrument that caters for both VKAs and DOACs, and contemporary data regarding knowledge and adherence to anticoagulants in Australian patients with AF. The purpose of this thesis was to address these gaps and contribute to the quality use of oral anticoagulants in AF.

1.3 Aims

The general aim of this thesis was to assess the level of anticoagulation knowledge and adherence in patients with atrial fibrillation in Australia.

The specific objectives were to:

i) Develop and validate a new OAC knowledge instrument that caters for both VKAs (warfarin) and the DOACs.

ii) Use this instrument to investigate the relationships between OAC knowledge, adherence and health literacy in patients with AF.

iii) Determine the level of OAC knowledge in patients with AF taking OAC therapy (either warfarin or a DOAC), identify any domains where significant knowledge gaps exist, and assess the association between patient-related factors and OAC knowledge.

iv) Estimate the proportion of patients who are non-adherent to OAC and identify predictors of adherence, and to determine if patient-related factors vary across levels of adherence in patients with AF.

1.4 Theoretical background

The development of this thesis was guided by the Capability, Opportunity and Motivation Model of Behaviour (COM-B), which hypothesises that interaction between three components, Capability, Opportunity and Motivation (COM), influence the performance of Behaviour (B) (figure 2) (33). 'Capability' refers to the patient's capacity to engage in the required thought and physical processes that influences a behaviour. 'Opportunity' refers to factors that are outside of the patient that makes the performance of a given behaviour possible, while 'Motivation' refers to all brain processes that encourages and direct behaviour. Factors related to each of the three components, including knowledge of therapy, beliefs about treatment and outcome expectations were explored as they influence OAC adherence.

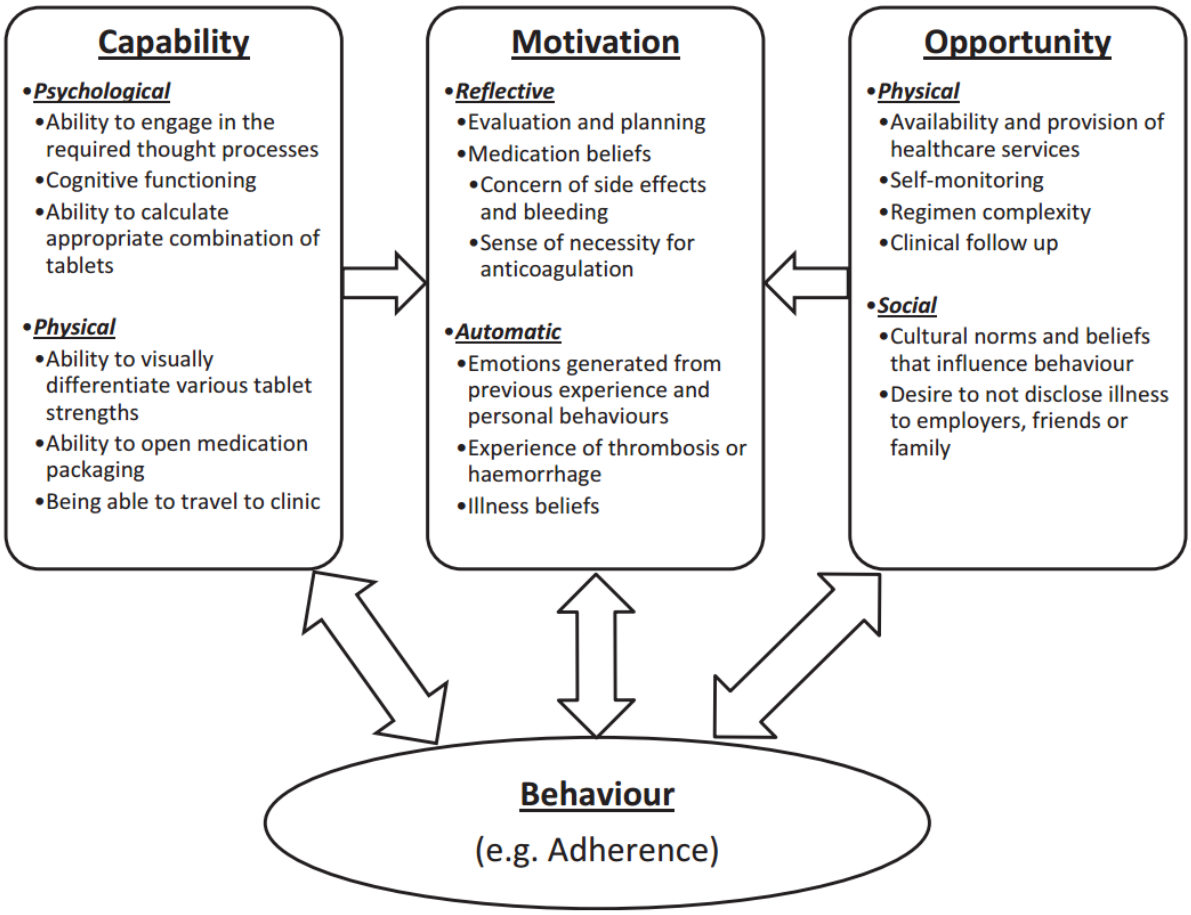

Figure 2: Capability, opportunity, motivation and behaviour (COM-B) model of adherence.

Adapted from Abdou *et al*, 2016 (33). Permission to reproduce granted by Wiley and Sons, Inc.

'Adherence' rather than 'compliance' was used throughout this thesis because it represents a philosophical shift which emphasizes partnership between patients and healthcare practitioners in order to ensure appropriate medication-taking behaviour.

CHAPTER TWO

2.0 Literature review

2.1 Anticoagulation knowledge in clinical practice

Overview

This section presents a review of the literature on OAC knowledge to identify the gaps in the literature relating to this area. It describes the approaches that have been employed to assess oral anticoagulant knowledge, the level of oral anticoagulant knowledge, and the association between knowledge levels and anticoagulation control as a surrogate marker of treatment outcomes. The results of this review suggest that OAC knowledge is suboptimal, and there is a need for the development of a new instrument that can assess knowledge related to both VKAs and DOACs.

2.1.1 Background

Patients with thromboembolic disorders often need to participate in shared decision-making with their healthcare practitioners and safely use oral anticoagulant (OAC) in order to achieve a favourable clinical outcome. However, shared decision-making and safe use of OAC by patients are difficult to implement without patients having an adequate knowledge of their therapy. The purpose of this review is to describe the approaches that have been employed to assess OAC knowledge, the level of anticoagulation knowledge, and the association between knowledge levels and treatment outcomes.

2.1.2 Introduction

Anticoagulants are recommended for the prevention and management of thromboembolic disorders (34). They act by preventing the formation of blood clots that could potentially result in life-threatening complications (34). Anticoagulants are a unique class of medication because their doses need to be optimised to provide a balance between antithrombotic benefit and haemorrhagic risk (35).

Patients with thromboembolic disorders need to participate in shared decision-making with their healthcare practitioners (36) and safely use their OAC medication (37) in order to achieve a favourable clinical outcome. However, shared decision-making (38) and safe use of OACs (39) by patients are difficult to facilitate without adequate knowledge of their therapy. Thus, patients need to be knowledgeable concerning their disease and treatment, including anticoagulant therapy.

Warfarin has a narrow therapeutic index, is associated with numerous food and drug interactions, and requires routine International Normalised Ratio (INR) monitoring (40). As such, patients using warfarin need to be knowledgeable around these topics in order to achieve optimal benefit from

their therapy, while minimising complications (41). Although patients using DOACs do not require routine coagulation monitoring, they also require adequate knowledge to enable them to take their medication safely. This is because the DOACs, like the VKAs, are also associated with increased risk of bleeding and their relatively shorter half-lives compared to warfarin could result in a loss of clinical effect after a short period of medication non-adherence (35). Due to the importance of knowledge in ensuring patient safety while taking OAC medication, a review of OAC knowledge is necessary to identify knowledge levels and patient characteristics associated with poor knowledge levels. As such, the purpose of this review is to describe the approaches that have been employed to assess OAC knowledge, the level of anticoagulation knowledge, and the association between knowledge levels and treatment outcomes.

2.1.3 Literature selection method

A literature search was conducted using MEDLINE and EMBASE databases from January 1980 to May 2017 for peer-reviewed publications. Studies related to patients' knowledge of OAC were selected. Search terms used were ''oral anticoagulant'', ''warfarin'', ''dabigatran'', ''rivaroxaban'', ''apixaban'', ''edoxaban'', in combination with ''knowledge.''

2.1.4 Eligibility criteria

Studies were included in this review if they were published in a peer-reviewed journal and if they focused on the use of anticoagulants in clinical practice. Additionally, included studies had to investigate one or more of the following: (i) the development of instruments to assess anticoagulation knowledge; (ii) level of anticoagulation knowledge in patients taking oral anticoagulant OACs; and (iii) the association between knowledge levels and treatment outcomes.

Editorial and articles that were not published in the English language were excluded from this review.

2.1.5 Results

Figure 3 shows the summary of the literature source and selection process. After duplicates were removed, 1,391 unique articles were identified from MEDLINE and EMBASE. After screening by title or abstract, the full text of 140 articles was assessed for eligibility, of which 103 were excluded. The main reason for excluding these studies was that they did not focus on OAC knowledge. A total of 37 articles comprising of instrument validation studies (Table 2), clinical trials, cross-sectional and prospective studies were included in this review (Table 3).

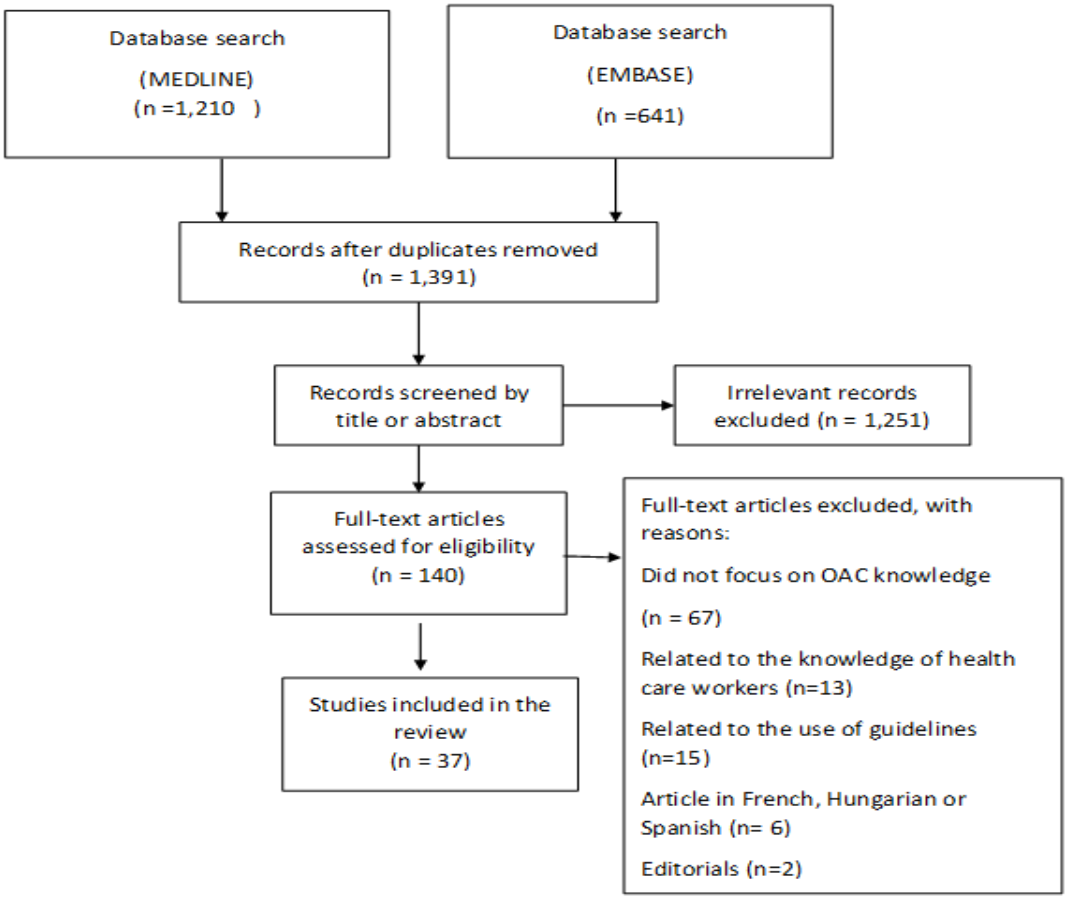

Figure 3: Flow chart of selection process

2.1.5.1 Vitamin K antagonist knowledge assessment instruments

Few studies have specifically focused on the development of instruments for assessing anticoagulation knowledge. In an early study, Taylor *et al* developed an instrument to assess anticoagulation knowledge using information available in a hospital guideline regarding

anticoagulation therapy (42). A major drawback of this instrument however, is that validity and reliability analyses were not conducted. These analyses are important requirement in the development of novel instruments to ascertain that such an instrument is measuring the intended construct, and it is able to provide consistent results (43). In later years, researchers have used diverse approaches to assess the validity and reliability of OAC knowledge instruments. Briggs *et al* reported on a study conducted in 60 patients from two anticoagulation clinics (44). Content validity was conducted using Marzano's taxonomy (45), while construct validity was evaluated by using a 31-item appropriateness checklist. The limitation of this study is that investigators did not mention if any reliability analysis was conducted. Zeolla *et al* conducted a study in 74 respondents taking warfarin and 27 age-matched subjects who were not taking warfarin (46). In this study, both validity and reliability tests were conducted (Table 2). The final instrument, called the Oral Anticoagulation Knowledge Test (OAK), has been subsequently validated in the Brazilian (47) and Malaysian populations (48).

Table 2. Instruments developed for the assessment of oral anticoagulant knowledge					
	Reference	**Sample size**	**Participants characteristics**	**Description**	**Validity and reliability test**
1	Taylor *et al* (42)	70	Patients newly referred to OAC clinic (54% aged less than 46 years)	20-item	None reported
2	Briggs et al (44)	60	60 English speaking patients currently receiving pharmacist-managed OAC education in community pharmacies (mean age of 63 years)	29-item (AKA)	Content validity, construct validity
3	Zeolla *et al* (46)	101	74 participants taking warfarin and 27 age-matched participants not on warfarin therapy recruited from community pharmacies, supermarket pharmacies, and anticoagulation clinics	20-item (OAK)	Content validity, construct validity, internal consistency reliability and test-retest reliability

4	Praxedes *et al* (47)	201	Patients taking warfarin for at least one year recruited during the service office-hours of an anticoagulation clinic, aged 18 years or older	Brazilian version of OAK	Construct validity, internal consistency reliability test-retest reliability
5	Matalqah *et al* (48)	382	Patients taking warfarin for at least six months, over 18 years of age, recruited from two Malaysian hospitals and able to communicate in the Malaysian language	Malaysian version of OAK	Construct validity, internal consistency reliability test-retest reliability
OAC Oral anticoagulant, OAK Oral Anticoagulation Knowledge Test, AKA Anticoagulation Knowledge Assessment					

2.1.5.2 Assessment of anticoagulation knowledge in clinical practice

2.1.5.2.1 Cross-sectional studies

The majority of studies that have been conducted to evaluate OAC knowledge in clinical practice have employed a cross-sectional design (27, 29, 49-68). Although it is difficult to compare the

findings of these studies, as they have used different instruments to assess knowledge, the mean reported scores have ranged from 36% to 75% (Table 3).

Many cross-sectional studies have utilised non-validated instruments. A study by Wang *et al* reported a knowledge score of 60% ± 21% (mean ± SD), with less than 50% of participants correctly answer questions related to food and medications interactions with warfarin therapy (65). In a similar study by Tang *et al*, a mean knowledge score of 48% ± 18% was recorded, with only 18% of participants having a score of ≥ 70% (29). Other studies that have reported similar mean scores to these studies include Davis *et al* (27), Smith *et al* (68) and Nadar *et al* (59) (Table 3) .

Researchers have also categorised OAC knowledge into three levels, using different and arbitrary cut-off values. Alphonsa *et al* divided respondents into three levels: <50% for poor knowledge, 50% to 70% for average knowledge, and >70% for adequate knowledge.(49). The study reported that 50% of the respondents had poor knowledge, 37% had an average knowledge, and only 13% of participants had adequate knowledge. In another study by Rocha *et al* involving participants with mechanical valve prostheses, OAC knowledge was stratified into three levels: (i) a score of ≤4 for inadequate knowledge, (ii) >4 to ≤ 8 for moderate knowledge, and (iii) >8 to 10 for adequate knowledge (60). The study reported that the majority of the patients (62%) had moderate knowledge, 36% patients had adequate knowledge, and only 2% had inadequate knowledge.

Two studies using an online survey to assess OAC knowledge have reported knowledge gaps in patients taking OACs. A survey conducted by the European Heart Rhythm Association reported that while over 90% of respondents knew the reason they had been prescribed an oral anticoagulant, only 21% of those taking DOACs knew that renal function testing at least once a year is important to assess their renal function (69). Using an online survey, Shuaib *et al* reported that more than

50% of participants taking OACs were unaware of any potential drug reactions or adverse effects related to OAC therapy (62).

Cross-sectional studies that have employed the use of a validated instruments have also reported suboptimal OAC knowledge in patients taking OACs (Table 3). Khudair *et al* conducted a study in patients taking warfarin for two or more months using a modified OAK questionnaire (55). The study reported that participants had the lowest knowledge score concerning the consequences of non-adherence (42%) and the interaction of warfarin with other medications (36%). In another study by Shrestha *et al* using the AKA instrument, 94% of participants were reported to possess inadequate knowledge defined as a score of at less than 72% (50). Lastly, a study by Baker *et al* using the AKA instrument, reported a mean score of 78%, of which 74% of respondents had adequate knowledge (70).

Demographic characteristics that have been weakly associated with patients' OAC knowledge include age of participants and level of education. In the study conducted by Rocha *et al*, the age of participants was inversely associated with knowledge score ($r = -0.248$; $p = 0.009$) (60). This finding has been supported by other authors, including Hu *et al* (52) and Chenot *et al* (51). Another study conducted by St-Louis *et al* reported a significant positive correlations between knowledge score and the educational level of respondents ($r = 0.10$; $p = 0.02$) (63). Other studies that have reported a similar association between educational level and OAC knowledge include studies by Mayet *et al* (56), and Yahaya *et al* (66) (Table 3).

Table 3. Oral anticoagulant knowledge in clinical practice									
	Reference	**Medication**	**Instrument description**	**Participants and setting**	**Method**	**N**	**% with AF**	**Result**	**Key limitations**
Cross-sectional studies									
1	Wang *et al* (65)	Warfarin	11-Item	Patients visiting anticoagulation clinic over a period of six months	Face-to-face interview	183	12	- Mean knowledge score of 60% - 64% of participants were unaware of medicines that interact with warfarin	-Single centre study -Use of non-validated instrument
2	Shuaib *et al* (62)	Warfarin	20-item	Patients visiting hospital over a period of three months	Online survey	200	NS	- 56% of respondents were unaware of potential drug interactions - 58% of respondents unaware of adverse effects of warfarin therapy	-Single centre study -Use of non-validated instrument
3	Nadar *et al* (59)	Warfarin	9-item	Patients who had attended anticoagulation clinics of three hospital at least six times	Face-to-face interview	180	NS	- Mean knowledge score of 61% - 46 % of participants were unaware of the dose and the indication for warfarin therapy	-Use of non-validated instrument
4	Tang *et al* (29)	Warfarin	9-item	Patients visiting anticoagulation clinic over a period of eight weeks	Face-to-face interview	122	39	- Mean knowledge score of 48% - 18% had a score of ≥ 70%	-Use of non-validated instrument
5	Shrestha *et al* (61)	Warfarin	AKA test (29-item)	Patients who visited the outpatient pharmacy of a hospital, and had been taking warfarin for at least 2 months	Face-to-face interview	34	NS	- 94% of respondents had a knowledge score of < 72% - 68% of respondents reported a knowledge score of < 50%	- Small sample size -Single centre study

6	Hu *et al* (52)	Warfarin	20-item	Patient who had undergone heart valve replacement	Telephone survey	100	NS	- Mean score of 71% - Advancing age was negatively associated with knowledge scores	-Use of non-validated instrument
7	Khudair *et al* (55)	Warfarin	Modified OAK test (22-item)	Patients attending anticoagulation clinic, and taking warfarin for at least two months	Self-administered	140	43	-58% of respondents were unaware of the consequences of non-adherence -64% of respondent were unaware of the interaction between warfarin other medications	-Single centre study
8	Moran *et al* (58)	Warfarin	22-item	Patients visiting an anticoagulation clinic	Self-administered	181	NS	- 33% of participants knew more than one medication that can affect warfarin therapy - 57% of participants were unaware of any potential side effects with warfarin therapy	-Use of non-validated instrument -Single centre study
9	Baker *et al* (50)	Warfarin	AKA test (29-item)	Patients who had been enrolled in an anticoagulation clinic for at least six months	Self-administered	185	61	- Mean score of 78% - 74% of respondents had a score of ≥72%	-Single centre study
10	Wilson *et al* (70)	Warfarin	20-item	Patients visiting an anticoagulation clinic	Face-to-face interview	65	NS	- Mean score of 70% - 50% of participants were knowledgeable regarding the side effects of warfarin therapy	-Single centre study -Small sample size
11	Alphonsa *et al* (49)	Acenocoumarol, warfarin and dabigatran	25-item	Patients taking OAC who were attending the Neurology and Cardiology clinic	Self-administered	240	NS	- 50% of the respondents had poor knowledge - 37% had an average knowledge level - 13% of participants had adequate anticoagulation knowledge	-Use of non-validated instrument

12	Chenot *et al* (51)	Phenprocoumon	13-item	Patients in general practice setting	Self-administered	345	70	- 75% of participants were unaware that the effectiveness of OAC could be affected by non-prescription medicine - Advancing age was negatively associated with knowledge score	-Use of non-validated instrument
13	Davis *et al* (27)	Warfarin	18-item	Patients attending two anticoagulation clinics	Self-administered	52	29	- The study reported a mean knowledge score of 60% - Only 37% percent of participants had a knowledge score of ≥ 70%	-Use of non-validated instrument -Small sample size
14	Rocha *et al* (60)	Warfarin	10-item	Patients visiting cardiology clinic of two hospitals	Face-to-face interview	110	NS	- 37% of participants did not know their INR target range - Advancing age was negatively associated with knowledge score	-Use of non-validated instrument
15	Van *et al* (64)	Fenprocoumon	10-item	Patients with congenital heart disease or acquired heart-valve defects recruited from several hospitals	Self-administered	57	NS	- 56% did not know that black-coloured stool is an indication of internal bleeding - 80% of respondents did not know that vitamin K could interact with their therapy	-Use of non-validated instrument -Small sample size
16	Smith *et al* (68)	Warfarin	52-item	Patients attending an anticoagulation clinic	Self-administered	100	100	- Participants recorded a mean score of 36%. - 93% of respondents did not know that vitamin K and herbal supplements could interact with their therapy	-Use of non-validated instrument

17	Jank *et al* (53)	Phenprocoumon	8-item	Patients attending an anticoagulation clinic	Self-administered	51	NS	- Respondents reported a mean knowledge score of 55%, - Knowledge score was not associated with anticoagulation control	-Use of non-validated instrument -Small sample size
18	St-Louis *et al* (63)	Warfarin	9-item	Patients who were 65 years or older with atrial fibrillation, and requiring OAC therapy for the first time	Self-administered	100	100	- Respondents reported a mean knowledge score of 53%, - No significant difference in knowledge scores between participants with poor and good anticoagulation control	-Use of non-validated instrument
19	Mayet *et al* (57)	Warfarin	8-item	Patients attending an anticoagulation clinic	Face-to-face interview	105	11	- 75% of participants had a score of ≥75% - Educational level of participants was associated with higher knowledge scores	-Use of non-validated instrument
20	Yahaya *et al* (66)	Warfarin	12-item	Patients who had made more than five visit to an anticoagulation clinic	Face-to-face interview	52	62	- Only 21% of participants had a knowledge score of > 80% - Educational level of participants was associated with higher knowledge scores	-Use of non-validated instrument -Small sample size
21	Hasan *et al* (67)	Warfarin	NS	Patients attending physician and pharmacist managed an anticoagulation clinics	Face-to-face interview	156	NS	- Respondents reported a score of 67% for knowledge related to the mechanism of action of warfarin	-Use of non-validated instrument

								- 43% for knowledge on the interaction between warfarin and alcohol	
22	Cheah *et al* (71)	Warfarin	14-item	Patient who were discharged on warfarin therapy	Telephone survey	50	NS	- Participants reported a mean score of 47% - Advancing age was negatively associated with knowledge score	-Use of non-validated instrument - Small sample size
23	Roche-Nagle *et al* (72)	Warfarin	NS	Patients attending an anticoagulation clinic	Face-to-face interview	150	18	- 28% of respondents were unaware of their indication for OAC therapy - 60% of respondents were unaware of the consequences of taking the wrong dosage of warfarin	-Use of non-validated instrument
Prospective studies									
24	Joshua *et al* (54)	Nicoumarol or warfarin	20-Item	Outpatient taking oral anticoagulant from a tertiary hospital	Face-to-face interview	101	NS	- Participants reported a mean knowledge score of 52.2% - 53% of the patients had a score of ≤ 50%	-Use of non-validated instrument
25	Janoly-Dumenil *et al* (73)	Fluindione, warfarin, or acenocoumarol	9-item	Patients who had been OAC for at least three months	Face-to-face interview	50	NS	- 70% of the respondents knew the name of their OAC - Only 24% of respondents knew their target INR levels	-Use of non-validated instrument
26	Winans *et al* (74)	Warfarin	OAK test (20-item)	Hospitalised patients who newly initiated warfarin therapy divided into intervention and usual care groups	Face-to-face interview	40	10	- The intervention group scored significantly higher on the OAK test than the usual care group (74% vs 55%; p = 0.004)	-Small sample size -Single centre study

27	Mavri *et al* (75)	Warfarin	12-item	Patients attending an anticoagulation clinic. Knowledge was assessed at baseline and after an educational intervention	Face-to-face interview	235	20	- Mean knowledge score improved from 68.8% to 81.3% two months after an educational material was provided to participants	-Use of non-validated instrument
28	Voller *et al* (76)	Warfarin	16-item	Patients from three centres. Knowledge was assessed at baseline (T0) and after an three educational intervention (T1, T2 and T3)	Self-administered	76	18	- Participants' mean knowledge score improved from T0 to T3: 40% (T0); 86% (T1), 94% (T2) and 96% (T3).	-Use of non-validated instrument -Small sample size
29	Cook-camp bell *et al* (77)	Warfarin	14-item	Patients taking warfarin and discharged from the hospital within the past two weeks.	Telephone survey	36	67	- Participants had a mean knowledge score of 56% - Only 33% of participants knew the correct action to take if they miss a dose	-Use of non-validated instrument -Small sample size
30	Lane *et al* (56)	Warfarin	14-item	Patients who have been diagnosed with AF for a period of three months or more. Knowledge was assessed at baseline and after an educational intervention	Face-to-face interview	93	100	- Only 57% knew that OAC medication is useful in preventing the formation of blood clot at baseline - Patients who were aware of their target INR range increased from 64% to 67% after the educational intervention	-Use of non-validated instrument
Clinical trials									

31	Stafford *et al* (78)	Warfarin	OAK test (20-item)	Patients discharged from eight hospitals and taking warfarin for at least three months. Patients were divided to receive usual care or an intervention involving OAC education	Self-administered	268	51	- Anticoagulation knowledge was significantly higher on day 8 in the intervention group compared to the usual care group (78% vs 65%; p < 0.001), - At 90 days post discharge, no significant difference was observed	- There may have been selection bias, as patients were recruited from selected hospitals
32	Maikranz *et al* (79)	Warfarin	13-item	Patients attending 52 general practices with lifelong indication for OAC therapy. Patients were randomised to receive usual care or an intervention involving OAC education	Self-administered	76	81	- A significant improvement was observed in the intervention group after 12 months (0.78 versus 0.04; p <0.001) - At 24 months, participants in the intervention group still had higher knowledge score, while the control group showed a slight decline (0.6 vs -0.3; p <0.001)	-Use of non-validated instrument - Small sample size
OAC oral anticoagulant, AF atrial fibrillation, INR International normalised ratio, NS not stated									

2.1.5.2.2 Prospective studies

Studies that have employed the use of a prospective design have also reported knowledge gaps in patients taking OAC. Prospective studies have been conducted to assess OAC knowledge in the outpatient setting, or to evaluate the impact of education on OAC knowledge. Joshua *et al* reported a mean score of 52%, with half of the respondents having a score of <50% in patients visiting a tertiary care teaching hospital (54). Similarly, Janoly-Dumenil *et al* reported that target INR levels and symptoms of medication overdose was known by only 24% and 22% of respondents in their study, respectively (73). Another study by Cook-Campbell *et al* reported a mean knowledge score of 56%, and only 33% of participants knew the correct action to take if they miss a dose (77).

Three prospective studies have evaluated the impact of education and training on anticoagulation knowledge. In a study by Mavri *et al*, respondents' knowledge was assessed at baseline, after which an educational booklet on OACs was provided (75). Two months later, anticoagulation knowledge was re-assessed to determine the effectiveness of the educational material. The mean knowledge score of participants improved from 68.8% to 81.3% ($p = 0.001$) (75). Similar results have also be observed in studies by Winans *et al* (74), Lane *et al* (56) and Voller *et al* (76), suggesting that an educational interventions could be useful in improving OAC knowledge.

2.1.5.2.3 Clinical trials

A non-randomised controlled trial was conducted by Stafford *et al* (78). The study compared warfarin knowledge in patients after hospital discharge who were either receiving usual care or an intervention that included warfarin education. Anticoagulation knowledge was assessed in the two groups on day 8 and 90 after hospital discharge, using the OAK test. The study reported that OAC knowledge was significantly higher on day 8 in the intervention group compared to the usual care group (78% vs 65%; $p <0.001$), however, at 90-days post discharge, no significant difference was

observed. In a cluster randomised controlled study by Maikranz *et al*, OAC knowledge was measured at baseline, and after 12 and 24 months in patients randomised into a control or intervention group (79). The intervention involved patient education, treatment monitoring and the provision of a patient-specific information leaflet. Although knowledge was similar for both the control and intervention group at baseline, a significant improvement was observed in the intervention group after 12 months (0.78 points versus 0.04 points; $p < 0.001$), and after 24 months (0.6 points versus -0.3 points; $p < 0.001$).

2.1.6 Association between knowledge levels and treatment outcomes

Few studies have investigated the relationship between anticoagulation knowledge and treatment outcomes. Available studies have essentially focused on the association between knowledge and anticoagulation control, with no study focusing on the incidence of stroke or bleeding events. Except for two studies, included studies have reported no association between knowledge levels and anticoagulation control. Tang *et al* reported a positive relationship between patients' anticoagulation knowledge and the number of INR values within the target range in the four most recent clinic visits ($r = 0.20$; $p = 0.024$) (29). In a second study by Khudair *et al*, participants with a knowledge score of ≥75% were reported to have a better anticoagulation control, defined as a minimum of five INR values within the therapeutic range out of six consecutive readings, compare to those with scores of <75% ($p < 0.001$) (55). A study by Baker *et al* employed three measures of anticoagulation control: (i) the number of INRs within therapeutic range, (ii) time in therapeutic range (TTR) determined using the Rosendaal method and (iii) the standard deviation of INR values (50). No significant correlation was observed between warfarin knowledge and any of the three measures of anticoagulation control. Similarly, studies by Rocha *et al* (60), Mayet *et al* (57), and

Nybo *et al* (80) have used different measures for anticoagulation control, and have all reported no association between anticoagulation control and knowledge levels.

2.1.7 Discussion

Validated and non-validated instruments have been employed to assess OAC knowledge in clinical practice, with most studies utilising non-validated instruments. Investigators have divided knowledge scores into two or three different categories and have mostly used arbitrary scores of 70%, 75% or 80% to signify adequate OAC knowledge. Studies have however not provided justification for these knowledge categories or cut-off values.

While knowledge levels appear to be generally suboptimal irrespective of participant characteristics and setting, no clear association between knowledge level and anticoagulation control was observed among the included studies. In addition, available studies have predominantly focused on warfarin therapy, with little attention given to DOACs.

Due to the frequent use of non-validated instruments, it is difficult to ascertain the extent of knowledge deficit in patients taking OAC. Nevertheless, knowledge deficiency was common regarding adverse effects, consequences of non-adherence, and food and drug interactions. Considering the complexity of OAC therapy, educational intervention is therefore important as part of the management strategy for patients taking OAC to help improve knowledge levels.

While advancing age and low educational level were consistently associated with poor OAC knowledge irrespective of study design, type of instrument and sample size, no consistent associations were observed with respect to other patient characteristics. Therefore, there is a need to focus on supporting elderly patients and those with limited formal education using simplified

educational resources. Some strategies that could be effective in this population include the use of multimedia and pictograms (81).

The included studies are not without their limitations. Most of the studies used a small sample size, cross-sectional methodology, and did not use a validated instrument. Furthermore, it is also possible that validated instruments were not able to cover all relevant knowledge domains, or not sensitive enough to detect a change in knowledge levels.

The relationship between OAC knowledge and anticoagulation control remains unclear. Although the majority of existing studies showed no association between the two variables, the lack of a consistent definition for adequate anticoagulation control makes it difficult to compare the results of the studies. As such, the relationship between knowledge levels and anticoagulation control is an area that requires further investigation. There is also a need for the development and validation of a simplified OAC knowledge instruments that caters for both warfarin and DOAC users. This would be useful in assessing patients' OAC knowledge in clinical practice and for research purposes. More studies with large sample sizes and a standardised definition of adequate anticoagulation control are required to evaluate the relationship between OAC knowledge and anticoagulation control. In addition, prospective studies should be designed to focus on the relationship between knowledge and other clinical outcomes, including the incidence of stroke and bleeding.

2.1.8 Conclusion

OAC knowledge is suboptimal in clinical practice and knowledge gaps are present across several domains. This suggests that educational intervention should be incorporated into the management strategy of patients taking OACs. Effort should also be made by healthcare practitioners to identify patients who are more likely to have significant knowledge deficit based on their clinical or

demographic characteristics, as candidates for more rigorous and structured educational interventions.

2.2 A summary of the literature evaluating adherence and persistence with oral anticoagulants in atrial fibrillation

Overview

This section summarises the literature regarding adherence and persistence with oral anticoagulants in the management of AF. It was conducted to understand the burden of non-adherence to OAC, and to aid the selection of a suitable approach to assess medication adherence in the subsequent studies reported in Chapters 4 and 6. The result of this review suggest that there is a need to improve adherence and persistence with anticoagulants in AF in order to optimise therapeutic outcomes. This review was published in the *American Journal of Cardiovascular Drugs* (https://www.ncbi.nlm.nih.gov/pubmed/27262433) on June 4, 2016.

2.2.1 Abstract

Atrial fibrillation (AF) is a growing public health concern and remains an independent risk factor for ischemic stroke. Warfarin, a commonly used oral anticoagulant, is associated with a 60–70 % relative reduction in stroke risk and a reduction in mortality of 26 %. However, warfarin has several limitations, including a narrow therapeutic window, variable dose response, multiple interactions with other drugs and concurrent illnesses, and the need for frequent laboratory monitoring. In recent years, the direct acting oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban and edoxaban, have been developed to overcome the limitations of warfarin therapy. These treatment strategies are either comparable or superior to warfarin in stroke prevention in AF. Despite the documented effectiveness of oral anticoagulants in AF, patients may not derive optimal benefit if they fail to adhere or fail to continue with their medication. This may lead to treatment failure, increased hospitalization and mortality. This review summarises the literature regarding adherence and persistence (or discontinuation) rates with oral anticoagulants in the management of AF; the impact of non-adherence and non-persistence on treatment outcomes; and the effectiveness of strategies to improve adherence and persistence with oral anticoagulant therapy.

2.2.2 Introduction

Atrial fibrillation (AF) is the most common form of arrhythmia in clinical practice and is associated with significant morbidity and mortality (82, 83). AF is a potent independent risk factor for ischemic stroke, and this risk increases with the presence of other cardiovascular risk factors (84). Patients with AF are five times more likely to have a stroke compared to the general population, and this category of stroke accounts for about 20% of the overall incidence of stroke (85).

Warfarin, a vitamin K antagonist (VKA), is associated with a 60-70% relative reduction in stroke risk and a reduction in mortality of 26%, (25). The directly acting oral anticoagulants (DOACs),

including dabigatran, rivaroxaban, apixaban and edoxaban, have been shown to be either comparable or superior to warfarin for stroke prevention in AF (86-89). Despite the documented effectiveness of these medications, patients will not derive optimal benefit if they fail to adhere or continue to take their medication.

Medication adherence has been defined as the "active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behaviour to produce a therapeutic result."(90) A closely related concept to adherence is medication persistence, which has been defined as "the duration of time from the initiation to discontinuation of therapy." (91) Both adherence and persistence have been classified as medication taking behaviour (91, 92).

Adherence can be measured using the direct and indirect method. Direct method involves the measurement of either the drug or its biological marker in body fluid, while the indirect method involves the use of self-reports, pill counts, prescription refill rate, electronic refill rate, assessment of clinical response and patient diaries (93). The direct methods are considered to be more robust than the indirect method, however are not practicable for routine clinical use(90) .

This review summarises the literature regarding adherence and persistence (or discontinuation) rates with anticoagulant in the management of AF; the impact of non-adherence and non-persistence on treatment outcomes; and the effectiveness of strategies to improve adherence and persistence with oral anticoagulant therapy.

2.2.3 Literature selection method

A literature search was conducted using Medline and EMBASE databases from January 1980 to March 2016 for English language peer-reviewed publications. Studies in clinical practice related to medication adherence and persistence with anticoagulants were selected. Search terms used

were “atrial fibrillation”, “oral anticoagulants”, “warfarin”, “dabigatran”, “rivaroxaban”, “apixaban”, “edoxaban”, “time in therapeutic range (TTR)” and “International Normalised Ratio (INR)” in combination with “adherence”, “non-adherence”, “persistence” and “discontinuation.”

2.2.4 Eligibility criteria

Studies were included in this review if they were published in a peer-reviewed journal between 1980 and 2016; if they focused on the use of anticoagulants in AF; and available in English language. Additionally, included studies had to investigate one or more of the following: (i) adherence and/or persistence with the use of oral anticoagulants (VKAs and DOACs) in the management of AF, (ii) the impact of non-adherence and/or non-persistence on treatment outcomes (stroke, bleeding and mortality), and (iii) strategies to improve adherence and/or persistence with oral anticoagulant therapy. Studies that included adherence acetyl salicylic acid (ASA) as a study drug in AF were excluded for two reasons: (i) ASA is an over-the-counter medication, therefore quantifying adherence is problematic, and (ii) the use of ASA for the prevention of stroke in AF is now discouraged by major guidelines (94, 95).

2.2.5 Results

Figure 4 shows the results of the selection process. The titles of 2,085 articles from the electronic databases search were reviewed, after which 1993 articles were excluded. The full text of 92 articles was reviewed, of which 62 studies were excluded. The major reasons for excluding these studies were that they either focused on adherence with clinical guidelines, or included aspirin as a study drug. A total of 30 articles including 8 randomised control trial and 22 cohort studies were included in this review (Table 4). Table 5 summarises the discontinuation rates of oral anticoagulants in randomised controlled trials (RCTs) that compared the DOACs with warfarin. Five RCTs were included: RE-LY, 2009, ROCKET-AF, 2011, J-ROCKET AF, 2012,

ARISTOTLE, 2011 and ENGAGE AF TIMI 48, 2013 (86-89, 96). Table 6 summarises the adherence rate with oral anticoagulant in clinical practice. The result of 9 retrospective (28, 97-104), 1 prospective (105) and 3 cross sectional studies were included (27, 106, 107). Table 7 summarises the persistence rate with oral anticoagulant in clinical practice. This consists of 10 retrospective (103, 104, 108-115) and one prospective study. Table 8 summarises the impact of poor medication taking behaviour on treatment outcomes. The result of two retrospective studies were included (28, 102). Lastly, table 9 summarises the result of three RCTs designed to improve medication adherence in patients taking oral anticoagulant (116-118).

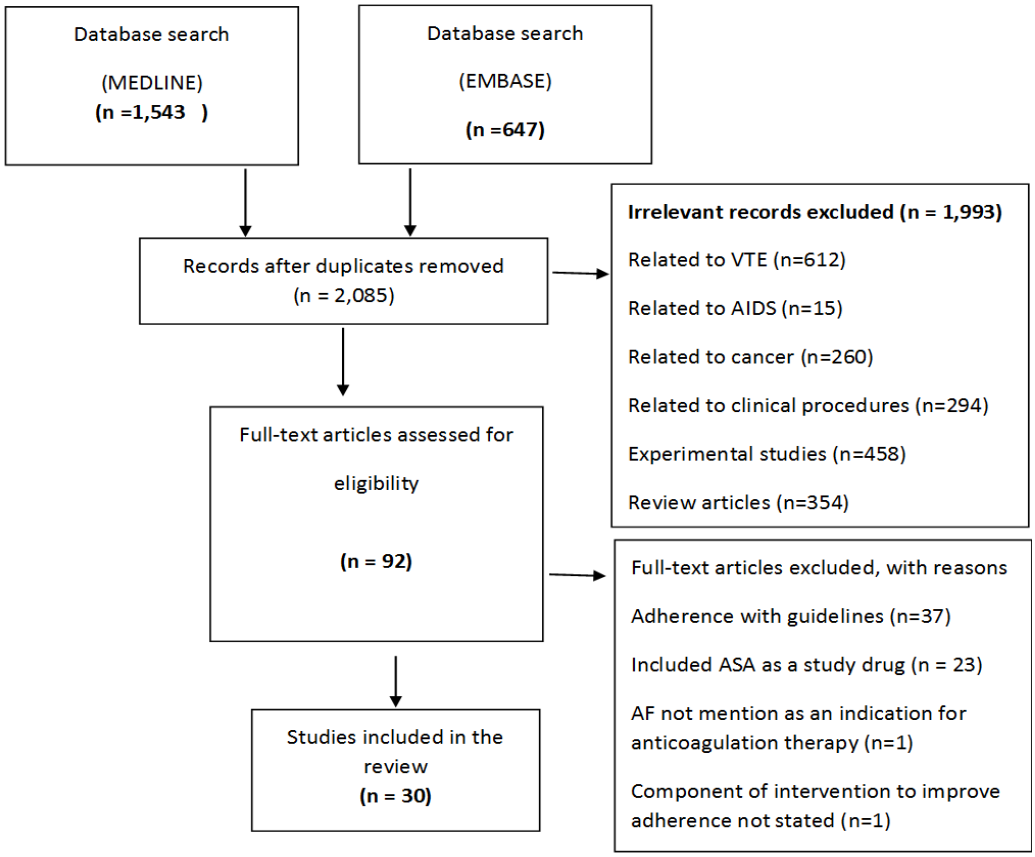

Figure 4: Flow chart of selection process

AF atrial fibrillation, AIDS acquired immune deficiency syndrome, ASA acetyl salicylic acid, VTE, venous thromboembolism.

Table 4. Evaluation of included articles (n=30)				
Study	**Adherence**	**Persistence (or discontinuation)**	**Impact of non-adherence on treatment outcomes**	**strategies to improve adherence and/or persistence**
Randomised controlled trials				
RE-LY (86)		✔		
ROCKET-AF (88)		✔	✔	
J-ROCKET AF (96)		✔		
ARISTOTLE (87)		✔		
ENGAGE AF TIMI (89)		✔		
Hedegaard *et al* (117)				✔
Clarkesmith *et al* (119)				✔
Kimmel *et al* (118)				✔
Prospective cohort studies				
Kimmel *et al* (30)	✔			
Beyer-Westendorf *et al* (105)		✔		
Retrospective cohort studies				
Shore *et al* (102)	✔			
Gorst-Rasmussen *et al* (100)	✔			
Cutler *et al*, (99)	✔			
Beyer-Westendorf *et al* (97)	✔			
Mchorney *et al* (101)	✔			
Zhou *et al* (104)	✔	✔		
Crivera *et al* (98)	✔			
Tsai *et al* (103)	✔	✔		
Gomes *et al* (109)		✔		

Fang *et al* (108)		✔		
Song *et al* (114)		✔		
Nelson *et al* (112)		✔		
Laliberte *et al* (110)		✔		
Zalesak *et al* (115)		✔		
Martinez *et al* (111)		✔		
Shiga *et al* (113)		✔		
Yao *et al* (28)	✔		✔	
Cross sectional				
Schulman *et al* (107)	✔			
Davis *et al* (27)	✔			
Castellucci *et al* (106)	✔			
For the present review, adherence was operationalised as taking medication as prescribed, while persistence as the proportion of patient who remained on oral anticoagulant therapy for a specified duration.				

2.2.6 Medication taking behaviour in clinical trials in AF

A number of randomised controlled trials involving anticoagulants have been conducted in patients with AF (Table 5). Although the methodologies of these trials varied considerably, the reports suggest that even in well-controlled trial situations, up to 35% of participants discontinued their medication (86-89, 96). The major reasons to which medication discontinuation has been attributed are the occurrence of an outcome event, adverse effects and withdrawal of consent by the participants.

The discontinuation rates for rivaroxaban, apixaban and edoxaban were similar to those of warfarin in the ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48 trials, with recorded rates of 24% vs 22%; 28% vs 25%; and 34% vs 34%, respectively (86-89). The discontinuation rate with

dabigatran was significantly higher than warfarin ($p < 0.001$) in the RE-LY trial, with rates of 21% in both the 110mg dabigatran and 150mg dabigatran groups, compared with a rate of 17% in the patients taking warfarin therapy. The higher discontinuation rate with dabigatran was attributed to the incidence of adverse events including hepatobiliary disorders, and adverse reactions including dyspepsia, which occurred at significantly higher rates in the dabigatran arm compared with the warfarin arm of the trial (86) .

Non-adherence rates have not been specifically recorded in any of the AF trials, but it is generally expected that the study methodologies will attempt to ensure optimal adherence in both the treatment and control arm in order to achieve an unbiased comparison. The time in therapeutic range (TTR) has been recorded in trials that included warfarin and a value of 60% or higher has been generally accepted as adequate (120). A TTR value of 64% was recorded in the RELY trial; 55% in ROCKET-AF; 62% in ARISTOTLE; and 65% in ENGAGE AF-TIMI48. TTR is a measure of anticoagulation quality with warfarin therapy and may be considered as a proxy for adherence, although it is recognised that it can be affected by a range of other factors apart from medication non-adherence. (121, 122).

The outcomes of patients who discontinued anticoagulant therapy were not captured in the majority of clinical trial reports. An exception to this was the ROCKET-AF study which was designed to assess the non-inferiority of rivaroxaban compared to warfarin in stroke prophylaxis in AF (88). The trial was carried out in a cohort of 14,264 patients randomly assigned to either adjusted warfarin or rivaroxaban therapy and followed up for a median period of 1.9 years. Patients who discontinued warfarin therapy or rivaroxaban therapy, of whom about half subsequently commenced a vitamin K antagonist, were followed up for a median period of 117 days for the occurrence of the study endpoint. The primary endpoint of stroke occurred in 81 patients in the

rivaroxaban group (4.7% per year) compared with 66 patients in the warfarin group (4.3% per year) (p =0.54). These recorded event rates (4.7% and 4.3) were higher compared to the total event rates of 1.7% and 2.2% per year for rivaroxaban and warfarin, respectively, recorded in the main study. The higher events rates in patients who discontinued anticoagulant therapy may be due to the complexity of managing high risk patients with AF who are unable to tolerate anticoagulation therapy, and this highlights the need for a particular focus on optimal anticoagulation coverage in this group of patients (123).

Table 5. Comparison of Medication Discontinuation Rates in AF Trials Involving the Direct Oral Anticoagulant

S. No.	Trial acronym [year]	Follow Up Period (years)	Drugs	No. of patients	Mean/Median age (years)	Discontinuation rate (%)
1.	RE-LY (86)	2.0	DAB 110mg	6015	72	21
			DAB 150mg	6076		21
			Adjusted WAR	6022		17
2.	ROCKET-AF (88)	1.9	RIV	7131	73	24
			Adjusted WAR	7133		22
3.	J-ROCKET AF (96)	2.5	RIV	639	71	15
			Adjusted WAR	639		13
4.	ARISTOTLE (87)	1.8	API	9120	70	28
			Adjusted WAR	9081		25
5.	ENGAGE AF TIMI 48 (89)	2.8	EDO 30mg	7034	72	33
			EDO 60mg	7035		34
			Adjusted WAR	7036		34

AF atrial fibrillation, *API* apixaban, *DAB* dabigatran, *EDO* edoxaban, *RIV* rivaroxaban, *WAR* warfarin

2.2.7 Medication-taking behaviour in clinical practice in AF

2.2.7.1 Assessment of adherence and persistence with anticoagulants in clinical practice in AF

Four major approaches have been used in quantifying adherence levels in clinical practice. These are medication possession ratio (MPR); proportion of days covered (PDC); patient self-report; and

medication event monitoring system (MEMS). The MPR is defined as the ratio of the number of days of medication supplied within the refill interval to the number of days in the refill interval, while PDC is defined as the ratio of the total number of days in which medication is available to the total number of days in the follow up period (124). Although both measures have been applied with a number of variations (125), a value of 80% or greater has been generally accepted as good adherence (90).Studies have also employed the use of patient self-report. These studies have employed the use of the Morisky medication adherence scale (MMAS), a validated tool originally designed to assess medication adherence with antihypertensive medication (126).

The fourth approach that has been utilised in the literature is the use of MEMS. MEMS are standard medication containers caps fitted with a microprocessor that records the number of times a pill bottle has been opened, after which data are then downloaded for display as a calendar of events (127). Persistence on the other hand is been quantified as the proportion of patient who remained on oral anticoagulant therapy for a specified duration.

2.2.7.2 Adherence to anticoagulants in clinical practice in AF

Attempts have been made to determine adherence rates with both warfarin and the DOACs in the management of AF in clinical practice (Table 6). A prospective study by Kimmel *et al* using medication event monitoring system bottle caps, showed that 40% of 136 participants on warfarin thromboprophylaxis followed for a mean period of 32 weeks had clinically significant levels of poor adherence (30). In this study, poor adherence was defined as having >20% missed doses or >10% extra doses. This translated into an increase in the risk of both under-coagulation and over-coagulation in non-adherent patients. In a multivariate analysis of the study data, significant associations were observed between under-adherence and under-coagulation, with a 14% increase in the odds of under-coagulation for every 10% increase in the number of times a pill bottle was

not opened (30). Also, participants who had extra pill bottle opening on more than 10% of study days were observed to have a significant increase in INR readings.

In another study by Davis *et al* involving 52 patients, the MMAS was used in assessing medication adherence with warfarin therapy. Adequate adherence with the MMAS is generally defined as a "no" response to all 4 questions, and inadequate adherence as a "yes" response to any of the four questions (126). Adequate adherence was reported by 50% (26) of participants, of which, only seven had good anticoagulation control. Among the other 26 participants who had inadequate adherence, none had good anticoagulation control. Statistical analysis of the study data showed a significant association between self-reported adherence and anticoagulation control ($p = 0.01$) (27). In a related study that also made use of the MMAS reported by Castellucci *et al*, 500 patients were surveyed, of which 74% (370) were on VKAs and 26% (130) on DOACs (rivaroxaban, dabigatran and apixaban). At the end of the study, adequate adherence was reported by 56% of patients taking the VKAs and 57% of patients taking the DOACs. A further analysis of the study data showed no significant difference occurred in adherence to twice daily vs once daily dosing of DOACs (106).

Studies have also been conducted with the use of dispensing and health care claim data. A cross-sectional study reported by Schulman *et al* recorded the highest adherence rate with dabigatran (107). In this study, pharmacy dispensing data were used to assess the adherence rate with dabigatran therapy in 103 patients taking dabigatran for at least 3 months. A median adherence rate greater than 99% was recorded in the study, and 11 (11%) patients were observed to have inadequate medication adherence with a MPR value of less than 80% (107). Shore *et al* have reported a similar finding with a larger population of 5376 patients taking dabigatran in a 12-month retrospective cohort study using the PDC approach. The study was conducted by using a national clinical data repository linked to data on dabigatran utilisation from a closed pharmacy system. A

median adherence rate of 94% was recorded and 28% of patients had a PDC of less than 80% (102).

Another study conducted by Gorst-Rasmussen *et al* in 2,960 patients newly diagnosed with AF, and taking dabigatran, reported a slightly lower PDC value. The study data were obtained by linking three national databases: a prescription registry with records of prescriptions purchased, a patient register with discharge diagnoses for all hospital admissions, and civil registration database with demographic information. At the end of the follow up period of 1 year, a mean PDC of 84% was reported, with over 75% of patients having a PDC value of > 80% (100).

A related study using the PDC approach investigated adherence to dabigatran therapy between a warfarin-naive cohort and a warfarin-experienced cohort. The study compared both groups by using administrative pharmacy claims data of 17,691 patients from a large pharmacy benefits scheme. At the end of the follow up period, the PDC for the warfarin-naive cohort was lower compared with the warfarin- experienced cohort (67.4% vs 71.2%) (103).

Lower adherence levels have also been reported with the DOACs. A study by Zhou *et al* investigated adherence with dabigatran using health claim data. The study included 2,713 patients with prevalent AF who were taking a single anticoagulant (non-switchers) throughout the study period. A mean MPR of 73% was reported for patient followed up for 6 months, which later reduced to 65% in patient followed up for a 1-year period (104). This relative lower adherence level with dabigatran therapy has also been corroborated by Cutler *et al* in a study involving 159 patients in who were not followed by an anticoagulation clinic. In this study medication adherence was assessed by evaluating prescriptions picked up at the local pharmacy. A mean adherence rate of 63% was reported using the MPR approach, and only 57% of patients had an adherence level of ≥80% (99).

Studies have also been designed to compare adherence among the DOACs. These studies have mainly focused on rivaroxaban, dabigatran and apixaban. A study by Mchorney *et al* investigated the pattern of adherence with the DOACs by using health claims data. This study was designed to compare adherence rates in 21,175 patients taking either, rivaroxaban, dabigatran or apixaban using the PDC approach. The result of the study showed that a higher proportion of rivaroxaban users had an adherence rate ≥ 80% compared to both dabigatran (73% vs 67%, p <0.001), and apixaban (73% vs 70%, p <0.001) users (101).

These findings have been supported in a study conducted by Crivera *et al* using health care claim data in 9,948 DOACs users. The proportion of patients with a minimum PDC of 80% was also higher for rivaroxaban users compared with both dabigatran users (75.4% vs 67.6%; p <0.001), and apixaban users (75.4% vs 70.6%; p = 0.076). Analysis of the population that switched from one DOACs to the other showed that those who switched to rivaroxaban still had a significantly higher proportion of patients with a PDC value of ≥80% compared to both dabigatran (76.9% vs 72.9%; p <0.001) and apixaban users (76.9% vs 71.3%; p = 0.037) (98).

A better adherence rate was also observed with rivaroxaban in a study by Beyer-Westendorf *et al* that made use of the MPR approach to compare adherence rate between rivaroxaban and dabigatran in primary care patients newly starting anticoagulant therapy. The study involved 7,265 and patients were followed up for at least 180 days and 360 days respectively from their first prescription date. The result of the study showed that a greater proportion of rivaroxaban users compared with dabigatran users had a MPR of ≥80% compared with dabigatran users (61.4% vs 49.5%, p <0.001), and a mean MPR of 76% and 69% respectively after 180 days (97). These results were also consistent for a follow up period of >360 days, with a greater proportion of rivaroxaban users having a MPR of ≥80% compared with dabigatran users (62.6% vs 47.6%, p

<0.001), and a mean MPR of 75% and 64% respectively. Lastly, a study by Yao *et al* using a retrospective analysis of administrative claims data from a large insurance database compared adherence with the DOACs as a group with the VKAs in 64,661 patients with AF newly initiating oral anticoagulant therapy. During the follow up period, a greater proportion of DOACs users compared with VKAs users had a PDC of ≥80% (47.5% vs 40.2%, p <0.001) (28).

The methods that have been used in assessing adherence in these studies are not without their limitations. MEMS can only record the number of times a pill bottle has been opened, but cannot determine if a pill been taken. Dispensing and claim data may have contained inaccuracies due to wrong entries, and it is also impossible to know if all supplied drugs has been taken by the patient. Nevertheless, these studies do provide evidence there is a need to improve medication adherence in AF in clinical practice, and that adherence with the once daily DOAC (rivaroxaban) is potentially better, than for the other DOACs.

Table 6. Adherence to Oral Anticoagulant in Clinical Practice											
	Reference	**Study design**	**Medication**	**Method**	**N**	**Age**	**(%) AF**	**Follow-up**	**Result**	**Inference**	**Key limitations**
1	Kimmel *et al* (30)	Prospective cohort study	WAR	MEMS	136	58.5	39*	0.62[a]	36% of patient had more than 20% missed pill bottle openings, and 4% had more than 10% extra pill bottle openings	Increase in the risk of both under-coagulation and over-coagulation occurred in non-adherent patients	-MEMS cap monitoring does not directly measure adherence
2	Schulman *et al* (107)	Cross-sectional study	DAB	MPR	103	75.5	100	NA	A median adherence rate greater than 99% was recorded in patients taking dabigatran	Adherence to dabigatran appears to be good	-MPR does not directly measure adherence -Single centre study
3	Shore *et al* (102)	Retrospective cohort study	DAB	PDC	5376	71.3	100	0.67[b]	A median adherence rate of 94% was recorded, and 28% of patients had a PDC of <80%	Adherence to dabigatran for a majority of patients appears to be optimal. However, 28% of patients had poor adherence	-Medication record may have contained inaccurate information -PDC does not directly measure adherence

4	Gorst-Rasmussen *et al* (100)	Retrospective cohort study	DAB	PDC	2960	72.1	100	1[a]	A mean adherence rate of 84% was recorded, with 75% of patients having a PDC value of > 80%	Adherence to dabigatran for a majority of patients appears to be optimal. However, 25% of patients had poor adherence	-PDC does not directly measure adherence -Findings may not be applicable in non-Danish population
5	Cutler *et al* (99)	Retrospective cohort study	DAB	MPR	159	70.7	100	1[c]	A mean adherence rate of 63% was observed and only 57% of patients showed an adherence rate of ≥80%	There is a need to improve adherence with dabigatran therapy	- Medication record may have contained inaccurate information MPR does not directly measure adherence
6	Beyer-Westendorf *et al* (97)	Retrospective cohort study	DAB &RIV	MPR	7265	74.5	100	1[b]	Mean adherence was higher for rivaroxaban compared with dabigatran (75% vs 64%; p <0.001)	Adherence appear to be better with rivaroxaban compared with dabigatran	- Medication record may have contained inaccurate information -MPR does not directly measure adherence
7	Yao *et al* (28)	Retrospective cohort study	WAR; DAB; RIV; API	PDC	64 661	73	100	1.10[b]	47.5% of DOACs patients had a PDC of ≥80%, compared with 40.2% in warfarin	A higher proportion of rivaroxaban patients had a PDC of ≥80%	- Medication record may have contained inaccurate information

									patients (p <0.001)		-PDC does not directly measure adherence
8	Mchorney *et al* (101)	Retrospective cohort study	DAB; RIV; API	PDC	21,175	76.1	78.7	0.88[a]	72.7% of rivaroxaban users had a PDC value of ≥80%, compared to dabigatran (67.2%; p <0.001) and apixaban (69.5%; p <0.001) users	A higher proportion of rivaroxaban patients had a PDC of ≥80%	- Medication record may have contained inaccurate information -PDC does not directly measure adherence
9	Zhou *et al* (104)	Retrospective cohort study	DAB	MPR	2713	63.0	100	1[c]	Adherence rate reduced from 73% to 65% within a year in patients taking dabigatran	There is a need to improve adherence with dabigatran therapy	- Medication record may have contained inaccurate information -PDC does not directly measure adherence
10	Davis *et al* (27)	Cross sectional study	WAR	MMAS	52	50.9	17	NA	Adequate adherence was reported by only 50% of participants	There is a need to improve adherence with warfarin therapy	-MMAS is a self-report instrument and does not directly measure adherence -Small sample size

11	Castellucci *et al* (106)	Cross sectional study	WAR; DAB; RIV; API	MMAS	500	63	18	NA	Adherence rate was 56.2% for patients on VKAs and 57.1% for patients on DOACs	There is a need to improve adherence with oral anticoagulant	-MMAS is a self-report instrument and does not directly measure adherence
12	Crivera *et al* (98)	Retrospective cohort study	DAB; RIV; API	PDC	9948	75.5	83.6	1[c]	75.4% of rivaroxaban users had a PDC value of ≥80%, compared to dabigatran (67.6%; p <0.001) and apixaban (70.6%; p >0.05) users	A higher proportion of rivaroxaban patients had a PDC of ≥80%	-PDC does not directly measure adherence - Medication record may have contained inaccurate information
13	Tsai *et al* (103)	Retrospective cohort study	DAB	PDC	17691	76.4	100	1[a]	PDC for the warfarin-naive cohort was 67.4% compared with 71.2% in the warfarin-experienced cohort	A lower adherence rate was observed in the warfarin-naive cohort	-MMAS is a self-report instrument and does not directly measure adherence

*API=apixaban, DAB=dabigatran, EDO=edoxaban, RIV=rivaroxaban, WAR=warfarin, NA=not applicable, MEMS=medication events monitoring system, PDC=proportion of days covered, MPR=medication possession ratio. a-mean; b-median; c-maximum, * Atrial fibrillation and/or flutter.*

2.2.7.3 Persistence with anticoagulants in clinical practice in AF

2.2.7.3.1 Persistence with warfarin

Medication persistence focuses on how long patients are able to continue with their medication, and can also affect treatment outcomes (91). The discontinuation rates for warfarin in patients with AF have been generally observed to be greater than 25% in the first year of therapy (Table 7) (108, 109, 114). Gomes *et al* reported on a large population-based cohort study of 125,195 new AF patients taking warfarin therapy over a 13-year study period (109). The study used multiple linked administrative databases to identify outpatient prescription records, hospitalisations, emergency department visits, physician services, patient demographics, and comorbidities for patients with a diagnosis of AF. The study showed that 8.9% of patients did not return for a refill after filling their first prescription, and 31.8% discontinued medication within the first year; this increased to 43.2% by the end of the second year (109).

In another study by Fang *et al*, 4,188 patients newly initiating warfarin in the Anticoagulation and Risk Factors in Atrial Fibrillation Study (ATRIA) were identified and followed up for about 5 years. Persistence with warfarin therapy was assessed using records from pharmacy and laboratory databases. The study reported a discontinuation rate of 26% at one year after the initiation of therapy, with an additional 3.6% of patients discontinuing warfarin therapy by the end of the third year (108).

In a third study by Song *et al*, administrative claims data were used in evaluating persistence and discontinuation pattern of long-term medications in patients with AF. The study included 16,036 patients who were prescribed warfarin within 3 months following AF hospitalisation. The investigators defined non-persistence as the presence of a ≥60-day gap in medication use, and permanent discontinuation as no evidence for the use of medication for ≥90 days until the end of

the study period. The result of the study showed that only 53.5% of patients were persistent with warfarin therapy for at least one year, and 42.6% of patients permanently discontinued therapy within the one year period (114).

2.2.7.3.2 Persistence with the DOACs versus warfarin

The majority of studies that have been conducted to date that have compared the persistence rate for DOACs with warfarin in patients with AF found that the DOACs were associated with improved medication persistence. A number of these studies have been conducted with the use of propensity score matching (PSM) technique in order to achieve a fair comparison amongst patients taking two different oral anticoagulants. Laliberte *et al* has reported on a study involving 18,270 patients with AF identified from health care claims data, newly commencing warfarin or rivaroxaban therapy (110). The patients were matched 1:4 for rivaroxaban and warfarin respectively. The result of the study showed that a greater persistence rate was observed with rivaroxaban compared with warfarin (82% vs 68%, $p < 0.0001$), during a follow up period of 6 months (110).

Another study by Nelson *et al* in newly anticoagulated patients using pharmacy claim data has reported a similar finding (112). In this study, 32,886 patients with AF were matched 1:1 for rivaroxaban and warfarin respectively, and followed up for a maximum duration of 3 years. The results showed that patients taking rivaroxaban had a higher persistence rate compared with patients taking warfarin (77% vs 58%). Also, in the subgroup of patients who did not switch anticoagulant therapy during the follow up period, a lower discontinuation rate of 16% was reported for the rivaroxaban arm compared with 42% in the warfarin arms (112).

In a third study by Zalesak *et al*, propensity score matching was used to identify 1,745 matched pairs of newly diagnosed AF patients taking dabigatran and warfarin, respectively. The persistence

rate was reported to be higher for dabigatran compared with warfarin at both 6 months (72% vs 53%, p <0.001) and one year (63% vs 39%, p <0.001) respectively (115). Lower persistence rates have however also been reported at both 6 months and 1 year with dabigatran. Tsai *et al* reported that 40% of patients discontinued dabigatran therapy within 6 months (103), while Zhou *et al* has reported that about 50% of patients discontinued dabigatran in the first year of therapy (104).

This increase in persistence with the DOACs has also been reported in studies that did not make use of the PSM technique. In a large study involving 27,514 anticoagulant-naive patients with incident AF, medication persistence was calculated based on the pattern of repeat prescriptions issued in a primary care setting. Persistence of VKA therapy fell from 76.5% to only 63.6% between 6 and 12 months, compared to a smaller fall from 85.9% to 79.2% for the DOACs (dabigatran, rivaroxaban and apixaban). After a follow up period of 12 months, the persistence rate was significantly higher with the DOACs compared to VKA for both the overall population, (79.2% vs 63.6%, p <0.0001), and for those with $CHA_2DS_2VASc \geq 2$ (83.0% vs 65.3, p <0.0001) (111).

A similar study was conducted by Beyer-westendorf *et al* to assess persistence with rivaroxaban, dabigatran, and VKA treatment in primary care patients newly starting anticoagulant therapy. The study involved 7,265 patients with persistence assessed during a follow-up period of 180 days and 360 days respectively after the first prescription date. Persistence rates were significantly higher in rivaroxaban users compare to both VKA (66% vs 58%; p <0.001), and dabigatran users (66% vs 60%, p <0.05) after 180 days. A similar trend was also observed after 360 days with persistence rates of 53%, 47%, and 25.5%, respectively for rivaroxaban, dabigatran and VKA respectively (97). The persistence rates observed with rivaroxaban does not seem to be affected by a history of warfarin exposure. A study by Beyer-Westendorf *et al*, in an ongoing prospective registry

involving more 2,600 patients, recorded similar persistence rates of 82% and 81% for patients switched from warfarin to rivaroxaban, and warfarin naive patients, respectively, during a median follow up period of 544 days. A discontinuation rate of 15% was observed for rivaroxaban in the first year of treatment (105), which is lower than the discontinuation rates of 26%, 30% and 32% recorded in large cohort studies involving VKAs (109, 128, 129).

Despite these reports of improved persistence with the DOACs, a study conducted by Shiga *et al* has reported a contrasting finding. In this study, persistence rates were compared in 401 patients with AF who had newly initiated DOACs, and 200 patients with AF who had newly initiated warfarin in the same period. During a maximum follow-up period of 24 months, 28% patients who had newly started DOACs and 17% patients who had newly started warfarin discontinued their medication. The persistence rates of patients prescribed DOACs was consistently lower than that of patients prescribed warfarin at 3, 6, and 12 months (85% vs 93%; 79% vs 88%; and 70% vs 82%, respectively). The major causes of DOACs discontinuation reported include drug adverse events, worsening renal dysfunction, and patients' desire (113).

These findings have suggested that a higher trend of persistence, although not uniform, with the DOACs for the majority of patients. However, non-persistence rates with all anticoagulants remain significant, and it is important to investigate the factors that may be associated with non-persistence in individual patients, and implement strategies to resolve them.

Table 7. Persistence with oral anticoagulant medication in clinical practice											
	Reference	**Study design**	**Medication**	**Definition of non-persistence**	**N**	**Age**	**%with AF**	**Follow-up (years)**	**Result**	**Inference**	**Key limitations**
1	Gomes *et al* (109)	Retro-spective cohort study	WAR	First instance of discontinuing warfarin therapy	125,195	≥66	100	5[c]	31.8% discontinued medication within the first year; this increased to 43.2% in the second year	Persistence with warfarin therapy among older patients with AF appears to be low	-Inability to determine if medication discontinuation was patient or physician initiated. Medication records may have contained inaccuracies or wrong information
2	Fang *et al* (108)	Retro-spective cohort study	WAR	>/=180 consecutive days off warfarin	4,188	71.8	100	4.6[b]	A discontinuation rate of 26% at one year. An additional 3.6% discontinued warfarin by the end of the third year.	1 in 4 patients newly starting warfarin for atrial fibrillation discontinued therapy in the first year	Medication records may have contained inaccuracies or wrong information

3	Song *et al* (114)	Retro-spective cohort study	WAR	A single medication gap of at least 60 days	16,036	73	100	1[c]	53.5% of patients were persistent with warfarin therapy for at least one year, and 42.6% of patients permanently discontinued therapy within the one year period	4 in 5 patients discontinued warfarin therapy with a year	- Medication records may have contained inaccuracies or wrong information
4	Nelson *et al* (112)	Retro-spective cohort study	WAR: RAV	A single medication gap of at least 60 days	32886	71.6	100	2.8[c]	A persistence rate of 77.1% was observed with rivaroxaban compared with 57.8% in patients on warfarin therapy (p <0.001)	Rivaroxaban demonstrated a trend towards better treatment persistence compared with warfarin	- Medication records may have contained inaccuracies or wrong information -Confounding may still have been possible even after propensity score matching
5	Laliberte *et al* (110)	Retro-spective cohort analysis	WAR; RAV	A single medication gap of at least 60 days	18,270	73.6	100	1.1[c]	Persistence rates were 81.5% with rivaroxaban compared with 68.3% in patients taking	Rivaroxaban demonstrated a trend towards better treatment persistence compared with warfarin	- Medication records may have contained inaccuracies or wrong information -Confounding may still have been possible even after

									warfarin (p <0.0001).		propensity score matching
6	Beyer-Westendorf *et al* (105)	Pro-spective cohort study	RIV	A gap of >4 weeks except for major surgeries	>2600	75.0	100	1.5[b]	Persistence rates were 82.0% and 81.1% for patients switched from warfarin to rivaroxaban, and warfarin naïve patients, respectively	Persistence with rivaroxaban therapy is similar in both groups.	-Registry may have introduced the possibility of a selection bias
7	Zalesak *et al* (115)	Retro-spective cohort analysis	WAR; DAB	A single medication gap of at least 60 days	3490	73.0	100	1.7[c]	Persistence rates were 72% vs 53% at six months (p <0.001), and 63% vs 39% at one year (p <0.001) for dabigatran and warfarin, respectively	Dabigatran demonstrated a trend towards better treatment persistence compared with warfarin	-Inability to determine if medication discontinuation was patient or physician initiated. Medications records may have contained inaccuracies or wrong information

8	Martinez *et al* (111)	Retro-spective cohort analysis	WAR; DAB; RIV; API	Discontinuation of the prescribed drug	27,514	74.2	100	1.9[a]	Persistence of VKA therapy fell from 76.5 % to 63.6 % between 6 and 12 months, compared with 85.9 % to 79.2 % for the DOACs	Rivaroxaban demonstrated a trend towards better treatment persistence compared with warfarin	Medications records may have contained inaccuracies or wrong information
9	Shiga *et al* (113)	Retro-spective cohort analysis	WAR; DAB; RIV; API.	Discontinuation of the prescribed drug	601	69.5	100	2[c]	Persistence rates were lower for patients prescribed dabigatran compared with patients prescribed warfarin at 3, 6, and 12 months (85% vs 93%; 79% vs 88%; and 70% vs 82% respectively)	Persistence rates with the DOACs were significantly lower than that of warfarin	-Small sample size -Medication records may have contained inaccuracies or wrong information
10	Zhou *et al* (104)	Retro-spective cohort study	DAB	A single medication gap of at least 60 days	2713	63.0	100	1[c]	Only 49% percent of patients were persistent with therapy at the end of a 1-year study period.	1 in 2 patients with prevalent AF discontinued dabigatran in the first year of therapy.	- Medication records may have contained inaccuracies or wrong information -Exclusion of patients with

											inadequate coverage
11	Tsai *et al* (103)	Retro-spective cohort study	DAB	A single medication gap of at least 30 days	17,691	76.4	100	0.5[a]	In the overall population, 40% of patients were non-persistent to dabigatran	2 in 5 patients discontinued dabigatran therapy within 6 months	- Short follow-up period - Medication records may have contained inaccuracies or wrong information
12	Beyer-Westen-dorf *et al* (97)	Retro-spective cohort study	VKAs; DAB; RIV;	A permanent discontinuation of therapy or a refill later than 60 days	7265	74.5	100	1[b]	Persistence rates were significantly higher in rivaroxaban users compared with both VKA (66.0% vs 58.1%; p <0.001), and dabigatran users (66.0% vs 60.3%, p <0.01) after 180 days	Rivaroxaban demonstrated a trend towards better treatment persistence compared with both dabigatran and warfarin	Medication records may have contained inaccuracies or wrong information

API APIXABAN, DAB DABIGATRAN, EDO EDOXABAN, RIV RIVAROXABAN, WAR WARFARIN, NA NOT APPLICABLE, MEMS Medication events monitoring system, PDC Proportion of days covered, MPR Medication possession ratio. a-mean; b-median; c- maximum.

2.2.8 The impact of poor medication-taking behaviour on treatment outcomes

There is a paucity of studies relating poor medication taking behaviour to treatment outcomes. However, the available studies in AF have shown that poor medication taking behaviour is associated with adverse treatment outcomes (Table 8). In a retrospective study of 5,376 patients taking dabigatran followed up for a median of 244 days, in which medication adherence was calculated using the PDC approach, a decrease in adherence of 10% was associated with a 13% increase in the combined outcome of all-cause mortality and stroke (102). These findings suggest the advantages of dabigatran relative to warfarin in terms of laboratory monitoring and reduced interactions must be balanced against the implications of non-adherence on treatment outcomes.

In a recent study by Yao *et al* involving 64,661 patients newly initiating anticoagulant (warfarin, dabigatran, rivaroxaban, or apixaban), multivariable Cox proportional hazards models was used in estimating the impact of non-adherence on the risk of stroke and bleeding (28). The result of the study showed that no significant effect was observed between non-adherence and the risk of stroke in patients with CHA_2DS_2VASc score 0 or 1 (28). However, in patients with CHA_2DS_2VASc score 2 or 3, not taking oral anticoagulant for ≥6 months was associated with an elevated risk of stroke (hazard ratio (HR) 2.73, 95% CI 1.76–4.23), compared with not taking oral anticoagulants for <1 week. A more pronounced association was observed in patients with CHA_2DS_2VASc ≥4, with HR of 1.96 (95% CI 1.48–2.60) for not taking oral anticoagulant 1 to 3 months; 2.64 (95% CI 1.93–3.61) for 3 to 6 months; and 3.66 (95% CI 2.68–5.01) for ≥6 months compared with not taking oral anticoagulants <1 week (28).

For overall bleeding risk, non-adherence to oral anticoagulant was generally associated with lower risk of bleeding. A hazard ratio of 0.46 (95% CI 0.25–0.86) was observed for not taking oral anticoagulant for ≥6 months in patients with CHA_2DS_2VASc score of 0 or 1; 0.68 (95% CI 0.52–

0.90) for patients with CHA_2DS_2VASc score 2 or 3, and 0.79 (95% CI 0.67–0.93) for patients with CHA_2DS_2VASc score ≥4.

An important finding of this study was that for patients with CHA_2DS_2VASc ≥2, better adherence was associated with lower stroke risk and a relatively small increase in bleeding risk, with no significant increase in intracranial bleeding. The findings of these studies suggest that better medication taking behaviour in the management of AF leads to improved treatment outcomes.

Table 8. Impact of poor medication-taking behaviour on treatment outcomes

	Reference	Study design	Medication	N	% AF	Age	Follow up	Result	Inference	Key limitations
1	Shore *et al* (102)	Retrospective study	DAB	5376	100	71.3	0.67[b]	A decrease in adherence of 10% was associated with a 13% increase in the combined outcome of all-cause mortality and stroke	The advantages of dabigatran relative to warfarin in terms should be balanced against the implications of non-adherence on treatment outcomes	Confounding variables not captured in database may have led to the observed association between adherence and outcomes
2	Yao *et al* (28)	Retrospective study	WAR	64661	100	73	1.1[b]	With CHA_2DS_2VASc score of ≥2, not taking oral anticoagulant for ≥6 months was associated with an elevated risk of stroke	Poor medication taking behaviour is associated with increased stroke risk in patients with CHA_2DS_2VASc score of ≥2	Confounding variables not captured in database may have led to the observed association between adherence and outcomes

DAB=dabigatran, WAR=warfarin, HR=hazard ratio, b-median, CHA_2DS_2VASc (presence of congestive heart failure, hypertension, age 65–74 y, age ≥75 y, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, sex category).

2.2.9 Effectiveness of strategies for improving medication-taking behaviour in AF

The literature has offered considerable evidence to suggest that adherence and persistence with anticoagulants in patients with AF need to be improved. Strategies to improve adherence and persistence with warfarin have resulted in mixed outcomes, and this suggests that a combination, and individualisation, of strategies may be required in different clinical practices and patient groups (Table 9). A randomised controlled trial by Hedegaard *et al* was conducted in patients with stroke or transient ischemic attack to investigate the impact of a multifaceted intervention in improving adherence to oral anticoagulant therapy, antiplatelets and statins in a hospital setting (117). A total of 203 patients participated in the study, with less than 10% of patients having a diagnosis of AF (117). The multifaceted intervention included motivational interviewing, medication review and follow-up telephone calls in patients in the intervention arm as compared to usual care in the control group. The investigators recorded a non-significant difference in MPR of 95% and 91% in the intervention and control arm, respectively.

However, in another randomised controlled trial by Clarkesmith *et al*, a marginal improvement in medication adherence was observed (116). This trial was conducted in 97 patients with AF newly prescribed warfarin, randomised to either usual care or the intervention arm of the study. The intervention arm consisted of a one-off educational session in which patients were shown a DVD of basic information on oral anticoagulation therapy pertaining to the risks, benefits and potential interactions with drugs and food (116). Patients in the intervention arm had a significantly higher TTR (76.2% vs 71.3%; $p = 0.035$) at 6 months which became non-significant at 12 months of follow-up (76.0% vs 70.0%; $p = 0.44$). This suggests potentially greater adherence to diet and lifestyle recommendations, as well as the medication itself, in patients receiving the educational intervention.

An additional study by Kimmel *et al* used a lottery-based incentive system in attempting to improve warfarin adherence (118). In this study, 100 participants were randomised to either a daily lottery where the daily reward ranged from $3 to $100 if they adhered to their medication regimen. In the study, 38% of patients had a diagnosis of AF and INR readings taken over the six months of the study were used as a proxy to assess warfarin adherence. At the end of the study, no significant difference in the percentage of out of range INRs was recorded between the two arms. However, the incentive system was found to significantly reduce out of range INRs in a subgroup with a low INR at baseline.

Table 9. Strategies to improve adherence with oral anticoagulants

	Reference	Study design	Medication	N	% AF	Age	Intervention	Result	Inference	Key limitations
1	Hedegaard *et al* (117)	RCT	WAR	203	<10	62.0	Motivational interviewing, medication review and follow-up telephone calls	A non-significant difference in MPR of 0.95 and 0.91 in the intervention and control arm, respectively.	No significant improvement was recorded between the intervention group and usual care	Participants in the study were not blinded and this may have been a source of bias
2	Clarkesmith *et al* (116)	RCT	WAR	97	100	72.9	One-off educational session in which patients were shown a DVD of basic information about anticoagulants	A significantly higher TTR of 76.2% vs 71.3% in the intervention and control arm, respectively.	This may suggest potentially greater adherence to diet and lifestyle recommendations, as well as to warfarin therapy	A number of participants refused to participate due to physical impairment
3	Kimmel *et al* (118)	RCT	WAR	100	38	61.8	Daily lottery reward from $3 to $100 if patient adhered to their medication regimen	The incentive system was found to significantly reduce out of range INRs in a subgroup with a low INR at baseline.	This may suggest potentially greater adherence to diet and lifestyle recommendations, as well as to warfarin therapy	It is possible that the expected value of the lottery was insufficient to motivate behavioural changes.

WAR=warfarin, RCT=randomised controlled trial, MPR=medication possession ratio, AF=atrial fibrillation, TTR=time in therapeutic range.

2.2.10 Further research

More studies are required in order to fully understand the impact of adherence and persistence with oral anticoagulants on treatment outcomes, and the most appropriate choice of oral anticoagulant for patients with poor medication taking behaviour. Prospective studies are better suited in achieving these objectives due to the fewer potential sources of bias and confounding compared with retrospective studies. A prospective study design will assist in determining the true picture of medication discontinuation (whether discontinuation of oral anticoagulant was by the patient or the physician, or whether it was in response to bleeding), and its impact on treatment outcomes. Prospective studies will also be useful in determining if patient medication preferences, perception of stroke and bleeding risk have a significant role in predicting poor medication taking behaviour.

Secondly, more randomised controlled trials are required in the literature to aid in identifying the best strategies for improving adherence and persistence with oral anticoagulants in specific patient populations.

Lastly, more studies are required to assess the impact of sub-therapeutic levels of the DOACs on treatment outcomes. This is important because the DOACs have short half-lives and are known to exhibit a rebound hypercoagulability effect. It therefore remains unclear if a minimum PDC or MPR value of 80% is acceptable as suggested in the literature, because missing a few doses of the DOACs may have a more severe effect on treatment outcomes compared to missing a few doses of warfarin with a long half-life.

2.2.11 Discussion and conclusion

The need for anticoagulant prophylaxis in AF will increase as the population continues to age. This review has considered the current adherence and persistence patterns with oral anticoagulants

in AF and the need for improvement in medication taking behaviour as a necessary step to improve patient outcomes. A detailed analysis of the data was not possible because of the inherent heterogeneity of available studies. However, adherence and persistence rates appears to be better with the DOACs compared to warfarin therapy, and as such, it could be assumed that their widespread use should be encouraged. However, non-adherence is currently difficult to detect in patients taking the DOACs because they do not require routine monitoring. This contrasts with warfarin management, where medication-related and/or lifestyle-related issues can be promptly identified during routine monitoring, after which, they can be potentially resolved. Given the current absence of such evidence, it is prudent to reinforce the need for medication adherence during every clinical interaction, irrespective of the anticoagulant patients are taking, and to explore other strategies of improving adherence and persistence in patients with AF.

CHAPTER THREE

3.0 Development and validation of an oral Anticoagulation Knowledge Tool (AKT)

Overview

This study aims to address the first objective of this thesis, which was to develop and validate a new OAC knowledge instrument that caters for both VKAs (warfarin) and the DOACs. The instrument was developed based on a review of the literature, feedback from anticoagulation experts, and testing in three different groups of participants. This study was published in *PlosOne* (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4924828/) on June 28, 2016.

3.1 Abstract

Background: Assessing and improving patients' anticoagulation knowledge can lead to better treatment outcomes. While validated knowledge instruments exist for use in people taking warfarin, these tools are not necessarily applicable to patients taking direct-acting oral anticoagulants.

Objective: To develop and validate an oral anticoagulation knowledge instrument that is applicable to all oral anticoagulant medications.

Methods: Ten anticoagulation experts participated in the development of the Anticoagulation Knowledge Tool to ensure content validity. The knowledge instrument was administered to three groups of participants comprising of 44 pharmacists, 50 patients and 50 members of the general public. A subgroup of participants in the patient and pharmacist group were retested approximately 2–3 months after the initial testing. Statistical tests were conducted to determine the validity and reliability of the scale, and item analysis was used to determine the performance of individual questions.

Results: The 28-item instrument developed had a scale content validity index of 0.92, supporting content validity. The pharmacist group's mean score was significantly higher than that of the patient group, and the patient group scored significantly higher than the general public group (94% vs 62% vs 20%, respectively; $p < 0.001$), supporting construct validity. Internal consistency reliability was acceptable with a Cronbach's α value of >0.7 across the three groups, and the test–retest reliability was confirmed with a Pearson's correlation coefficient of 0.72 and 0.78 for the pharmacist and patient groups, respectively.

Conclusion: The Anticoagulation Knowledge Tool is a valid and reliable instrument that can be used in routine clinical practice to assess patients' anticoagulation knowledge.

3.2 Introduction

Anticoagulants are widely used in the treatment and prevention of many thromboembolic disorders (130). Patients' knowledge of their medication and medical condition can affect treatment outcomes (131), and this becomes more critical in patients prescribed oral anticoagulants due to the narrow therapeutic indices of this class of medication, and the potentially devastating sequelae of both therapeutic failure and over-anticoagulation (50).

In the literature, attempts have been made to assess patient anticoagulation knowledge, and this has led to the development and use of a number of instruments in different settings. The earliest documented attempt to develop an instrument to evaluate patients' anticoagulation knowledge was by Taylor *et al*, in which a scale was developed based on information available in a district hospital guideline for managing patients taking warfarin (42). More recent attempts by researchers have developed scales based on the use of patient educational material, review of the literature and experts' opinion using either open ended or multiple choice questions (27, 29, 132). These scales have been used in a number of studies to establish the relationship between anticoagulation knowledge and treatment outcomes, and have yielded mixed results. Two of these studies have reported an association between adequate anticoagulation knowledge and positive treatment outcomes, (29, 132)while the other two have reported no association (27, 66). A major limitation of these studies, however, is that none of them have employed the use of an instrument which has been psychometrically validated.

To date, only the anticoagulant knowledge assessment (AKA) by Briggs *et al* (133) and the oral anticoagulant knowledge test (OAK) by Zeolla *et al* (134) have been developed and validated with regard to both content and construct validity. However, both OAK and AKA have been designed to assess knowledge regarding vitamin K antagonists (VKAs) and are not applicable to the direct

acting oral anticoagulants (DOACs). With the recent introduction of the DOACs (dabigatran, apixaban, rivaroxaban and edoxaban) into clinical practice, there is need for a validated instrument to assess patients' knowledge of their anticoagulation therapy that applies to both the VKAs and the DOACs. The objective of this study was to develop and validate a knowledge instrument that can be used in assessing anticoagulation knowledge related to all the available oral anticoagulant medications.

3.3 Methods

3.3.1 Anticoagulation Knowledge Tool development

We began by conducting a comprehensive review of the literature on patient anticoagulation knowledge, with additional information obtained from freely available patient educational material. The knowledge domain covered in the review of the literature included basic drug information, adverse drug effect, drug-drug interactions, drug monitoring and dietary issues. Similar information was then grouped to form a list of 56 items consisting of both open ended and multiple choice questions. The usefulness of each question in assessing anticoagulation knowledge was then discussed by the authors, after which the items were ranked on a scale of 1 to 5 (1 = strongly disagreed, 5 = strongly agreed) in terms of their relevance to anticoagulation knowledge. These rankings were used to eliminate irrelevant questions and create a 28-item draft instrument.

The items in the draft instrument were then discussed with 15 selected people from a non-medical background to ensure clarity of the sentences, simplify wording and to identify ambiguous and misleading terms. Items in the draft instrument were reworded based on the feedback received.

3.3.2 Content validity

Content validity refers to the degree to which a scale has an appropriate sample of items to represent the construct of interest (135). To ensure content validity, the draft instrument was presented to 10 anticoagulation experts (8 pharmacists and 2 physicians) selected based on their work experience or research related to the use of oral anticoagulants. These experts were asked to rate the relevance of each item on the draft instrument on a four-point ordinal scale (1= not relevant, 2 = somewhat relevant, 3 = quite relevant, 4 = highly relevant), and to suggest other items for the scale which may have been omitted. The content validity index for each item (I-CVI) and overall content validity of the scale (S-CVI) was then calculated using the method of Polit *et al* (135, 136). In calculating the I-CVI, the rating scale was dichotomised, with ratings of '1' and '2' combined as not relevant, and ratings of '3'and '4' combined as being relevant, while the S-CVI was calculated by determining the average of all the I-CVI values. Further, I-CVI values were translated into values of a modified kappa index (k*) to adjust for chance agreement among the experts participating in the content validity exercise. The modified kappa index was determined using the formula – k* = (I-CVI- pc)/ (1- pc), where pc refers to the probability of chance agreement among the experts and was computed using the formula for a binomial random variable, with one specific outcome (pc = [N! /A! (N - A)!] x 0.5^N; where 'N' = number of experts and 'A' = number of experts agreeing on relevance of an item). The average S-CVI of the scale was 0.92 with I-CVIs ranging from 0.6-1 and k* ranging from 0.5-1 (Table 10). The final instrument was divided into two sections – section 'A' and 'B', with section 'A' comprising general anticoagulation knowledge questions applicable to both the DOACs and VKAs, and section 'B' comprised of VKA-specific questions.

Table 10. Item and Scale Content Validity Indexes			
No.	**General questions**	**I-CVI**	**Modified kappa**
1	What is the name of your anticoagulant medicine?	1.00	1.00
2	Why has your doctor prescribed you this medicine?	1.00	1.00
3	How does this medicine work in your body?	0.70	0.66
4	How many times a day do you need to take this medicine?	1.00	1.00
5	For how long do you need to take this medicine (for example, 3 months, and 6 months, life-long)?	1.00	1.00
6	Why is it important to take this medicine exactly as your doctor has told you?	1.00	1.00
7	Is it acceptable to take this medicine at different times as long as you take it on the required days?	1.00	1.00
8	Is it acceptable to double the next dose of this medicine if you miss a dose?	1.00	1.00
9	Is it possible that skipping one dose of this medicine could worsen your condition?	0.90	0.90
10	Is it appropriate to stop taking this medicine once you feel better?	0.90	0.90
11	Is it safe to take anti-inflammatory medicines like ibuprofen (Nurofen® or Advil®) while you are taking this medicine?	1.00	1.00
12	Is it safe to take vitamin supplements and herbal medicines with this medicine without consulting your doctor?	0.90	0.90

13	Is there any benefit in taking more of this medicine than your doctor has told you to take?	0.80	0.79
14	Will drinking too much alcohol increase the risk of side effects with this medicine?	0.90	0.90
15	Is it necessary to inform a surgeon, dentist or other health professional that you are taking this medicine before undergoing surgery or a procedure?	1.00	1.00
16	Is it important that all the health care practitioners you see know that you are taking this medicine?	0.90	0.90
17	What is the most important side effect of this medicine?	0.80	0.79
18	Three signs of side effects that you should watch out for while taking this medicine are:	0.80	0.79
19	Three things you can do to reduce your risk of side effects are:	0.60	0.50
20	What is the best step to take if you accidentally take too much of this medicine?	1.00	1.00
	Question specific to people taking warfarin		
1	What is your target INR range?	0.90	0.90
2	What was your last INR reading?	1.00	1.00
3	Are routine INR tests necessary to know how well this medicine is working?	1.00	1.00
4	Is an INR value above your target range good for your general wellbeing?	1.00	1.00
5	Is it possible for INR values below your target range to be bad for your health?	0.90	0.90

6a	Is it possible for your diet to affect your warfarin therapy?	1.00	1.00
6b	If you answered 'Yes' above, list Three foods that can affect your anticoagulant therapy.	0.90	0.90
7	List one vitamin that can significantly affect your anticoagulant therapy.	0.80	0.79
pc (probability of a chance occurrence) was computed using the formula for a binomial random variable, with one specific outcome: **pc = [N!/A!(N - A)!]*0.5^N where N = number of experts and A = Number agreeing on good relevance. k* = kappa designating agreement on relevance, k* = (I-CVI- pc)/(1- pc).** **k* of 0.4-0.59 (fair); 0.60–0.74 (good); and > 0.74 (Excellent).** Average Scale-CVI= 0.92			

3.3.3 Pilot study

In order to further ensure readability and comprehension, a pilot study was conducted in 13 participants (5 pharmacists, 3 patients and 5 members of the general public) representing the three groups to be compared. The results from the thirteen pilot studies participants were not included in the main study. Instructions on completing and returning the questionnaire were further revised based on the feedback obtained in the pilot study. The final instrument used in the study is available in Appendix A6.

3.3.4 Validation study

Adults (aged > 18 years) who were able to read and complete the questionnaire independently were recruited into the validation study. All the participants in the validation study were recruited from Tasmania, Australia. Subjects were recruited into three groups comprising of a pharmacist

(expert) group, patient group and general public group. The pharmacist group was expected to serve as the positive control while the general public group was expected to serve as the negative control. Pharmacists were recruited from a total of 26 community and hospital pharmacies; patients currently prescribed oral anticoagulants were recruited from 14 community pharmacies; and participants from the general public group were recruited from 12 public places (e.g. parks, bus stops and shopping malls). Participants from the general public group were eligible to participate in the study if they were not health professionals, patients prescribed oral anticoagulants and did not have close relationships with patients taking oral anticoagulants. Information sheet for the study was provided to participants in the three groups which stated that anticoagulants are also called blood thinners, specifically to assist participants in the general public group who may be less familiar with the term 'anticoagulant.' Also, written informed consent was obtained prior to participation. Participants in the pharmacist and general public group were required to assume that they were currently taking an oral anticoagulant and answer the questions in both sections of the survey, while participants in the patient group were asked to respond to the survey based on the oral anticoagulant they had been prescribed by their physician. Patients who were prescribed any of the DOACS were required to answer the questions in section 'A' only, while patients who had been prescribed VKAs were asked to answer the questions in both sections. Participants in the pharmacist group were given the option of completing the test online or by using a paper format, while the other two groups completed the test by using only the paper format. Participants who preferred to use the paper format had the option of completing the survey on the spot, or return it using a reply paid envelope. The study protocol was reviewed and approved by the Tasmanian Health and Medical Human Research Ethics Committee.

3.3.5 Validity and reliability

Construct validity refers to the extent to which a measure adequately assesses the construct it purports to assess (137). Construct validity was assessed using the contrasted group approach which involves identifying two or more groups of individuals who are expected to have different scores on the characteristics being measured by an instrument (137). Using this approach, we hypothesised that the instrument would be sensitive to multiple levels of anticoagulation knowledge. Also, we expected the mean score of the pharmacist (expert) group to be higher than the mean patient group score, and the mean score of the patient group to be higher than that of the general public group.

Two reliability tests were conducted: test-retest reliability and internal consistency reliability. In order to ensure the instrument's stability, a re-test was conducted at approximately 2-3 month after the initial test administration, a time period considered sufficient to reduce the impact of recall. All the participants in the pharmacist and patient group were eligible for re-test, but only 32 participants in the patient group and 22 in the pharmacist group participated in the second test. Internal consistency reliability was also conducted across the three groups to ensure the inter-relatedness of the items in the instrument.

3.3.6 Scoring

Scoring was done use a dichotomous scale, with a score of '1' or '0' for each correct answer or wrong answer, respectively. A maximum score of '1' was allocated to each correct answer for all of the questions with the exception of item '6', '18' and '19' in section 'A' and item '6b' in section 'B'. A maximum score of '2' was obtainable for item '6' in section 'A' ('Why is it important to take this medicine exactly as your doctor has told you?') 1 mark each was allotted for answers related to the prevention of thromboembolism and answers related to minimising the risk of

bleeding. For items ‘18’ and ‘19’ (‘three signs of side effects you should watch out for’ and ‘three things you can do to reduce your risk of side effect’, respectively) 1 mark each was allotted for each correct sign of side effects to look out for, 1 mark each was allotted for three correct food substances mentioned. A maximum total score of ‘25’ was obtainable for patients taking the DOACs required to answer only section ‘A’ of the questionnaire, while a maximum total score of ‘35’ was obtainable for patients taking the VKAs (warfarin) required to answer both sections of the questionnaire. Final scores were presented as a percentage of correct answers for all the participants in the study.

3.3.7 Statistical analysis

Analysis of variance (ANOVA) was used in comparing the mean scores between the pharmacist, patient and general public groups, with $p < 0.05$ considered statistically significant. Pearson's correlation was used in determining the correlation between the test and re-test scores for the pharmacist and patient groups, and values between 0 and 0.49 were considered as ‘very low’ to ‘low’ correlation, while values between 0.5 and 1.0 were considered as ‘moderate’ to ‘very strong’ correlation. Cronbach’s alpha score was used in determining internal consistency reliability and across the three groups, with a score of 0.7 or greater considered acceptable (138). Lastly, the relative difficulty of each item and the instrument’s ability to discriminate between groups was also analysed by determining the differences in the percentages of items correctly answered across the three groups. Statistical analysis was conducted using SPSS Version 22.0.

3.4 Results

One hundred and forty-four participants, comprising 44 pharmacists, 50 patients and 50 members of the general public, participated in the validation study. Four surveys from the general public

group were excluded from the analysis due to participants being either health professionals or having experience with the use of oral anticoagulants; one survey from the patient group was excluded from the final analysis because the patient was not taking an oral anticoagulant at the time of the study. Overall, the results of 139 participants were included in the analysis (Table 11).

The mean score for the pharmacist (expert) group was significantly higher than that of the patient group, and the patient group's mean score was significantly higher than the general public group's ($p < 0.001$; Table 12). No statistically significant difference in score was observed between patients taking the VKAs and the DOACS ($p > 0.05$). For internal consistency reliability, a value of 0.92 was obtained in the general public group, 0.71 in the patient group for the general anticoagulation questions and 0.87 for participants taking warfarin required to answer both sections 'A' and 'B', and 0.73 in the pharmacist group (Table 13). Test-retest reliability was confirmed with a Pearson's correlation of 0.79 and 0.72 in the patient and pharmacist groups, respectively (Table 13). For the item analysis, item difficulty ranged from 0-100% across the three groups. The questions with the largest differences are listed in Table 14. Analysis of the patient group showed that patients taking the DOACs were less likely to view skipping a dose of prescribed oral anticoagulant as a problem compared to patients taking warfarin ($p < 0.05$). No significant difference was observed in test scores based on both the type of oral anticoagulant patients were taking, and the duration of anticoagulation therapy.

Although this study was not designed to assess the differences in test scores based on educational level, analysis of the general public group indicated that high school education or less was significantly associated with lower performance ($p < 0.01$). No other differences were observed based on any other demographic characteristics across the three groups.

Table 11. Demographic characteristics			
	General public (n= 46)	Patients (n= 49)	Pharmacists (n= 44)
Male n (%)	28 (64)	34 (69)	14 (34)
Age in years (mean +/- SD)	38 ± 11	74 ± 12	34 ± 10
Highest education completed n (%)			
High school	14 (30.4)	18 (36.7)	NA
College	8 (17.4)	5 (10.2)	NA
Technical/ Vocational	5 (10.9)	9 (18.4)	NA
Bachelor degree	5 (10.9)	11 (22.4)	35 (79.5)
Post graduate	13 (28.3)	5 (10.2)	9 (20.5)
No formal education	1 (2.2)	1 (2.0)	0 (0)
Duration of oral anticoagulant therapy	NA	< 3 months: 3 (6.1)	NA
		3-12 months: 4 (8.2)	
		1-2 years: 8 (16.3)	
		> 2 years: 32 (65.3)	
		Not reported: 2 (4.1)	
NA = Not applicable			

Table 12. Anticoagulation Knowledge Instrument Scores			
	General public (n=44)	Patient (n=49)	Pharmacist (n=44)
Mean (%)	19.9 ± 16.4	62.0 ± 13.9	93.7 ± 6.9
Minimum (%)	2.9	31.4	65.7
Maximum (%)	62.9	91.4	100
Statistics F (2, 136) = 359.8; p <0.0001			

Table 13. Validity and Reliability Coefficients			
	General public	Patient	Pharmacist
Internal consistency (Cronbach alpha)	(n=46) 0.92	(Section A) (n=49): 0.71 (Section A and B) (n=15): 0.87	(n=44) 0.73
Test –retest (Pearson's correlation)	NA	(n=32) 0.78	(n=22) 0.72
NA = Not applicable			

Table 14. Individual Item Analysis of Questions with Significant Variation Between Groups			
Item	General public (%)	Patient (%)	Pharmacist (%)
Why has your doctor prescribed you this medicine?	7.9	89.6	100
How does this medicine work in your body?	10.5	70.8	100
How many times a day do you need to take this medicine?	10.5	91.7	100
For how long do you need to take this medicine (for example, 3 months, and 6 months, life-long)?	10.5	91.7	100
Is it appropriate to stop taking this medicine once you feel better?	47.4	100	100
Is there any benefit in taking more of this medicine than your doctor has told you to take?	47.4	93.8	95.0
What is the most important side effect of this medicine?	2.6	60.4	100
What is the best step to take if you accidentally take too much of this medicine?	28.9	75.0	100
VKA (warfarin)-specific questions			
What is your target INR range?	0	93.3	95.0
What was your last INR reading?	0	93.3	95.0
Are regular INR tests necessary to know how well this medicine is working?	21.1	100	90.0

Is an INR value above your target range good for your general wellbeing?	2.6	66.7	90.0
Is it possible for INR values below your target range to be bad for your health?	10.5	80.0	87.5
Is it possible for what you eat to affect your warfarin therapy?	21.1	73.3	92.5

3.5 Discussion

We have described the development and validation of the Anticoagulation Knowledge Tool (AKT) - an instrument that allows for differences in anticoagulation knowledge to be measured that is applicable to patients taking both the VKAs and DOACs. The AKT is a 20-item knowledge questionnaire with eight additional questions for people taking VKAs (warfarin). Participants in the study were able to complete the survey independently, following written instructions, suggesting that the survey can be self-administered in routine clinical practice like existing tools such as the OAK and AKA. However, unlike the OAK and AKA, our AKT incorporates both open ended and multiple choice questions, as surveys with only multiple choice questions have the disadvantage of providing clues to the correct answers and increasing patients' total score (139). Participants who filled the survey on the spot spent between 10 -15 minutes, while the length of time for participants who prefer to use the reply-paid envelope option could not be ascertained. This suggest that the questionnaire can be completed in a relatively short period of time.

The method used in this study is consistent with recent consensus for the development and validation of new instruments. For content validity, a number of methods have been proposed for the content validation of new instruments including the T index (Tinsley & Weiss, 1975); Content

validity ratio 'CVR' (Lawshe, 1975); rWG index (James *et al*, 1984); CVI (Lynn, 1986) and r*WG index (Lindell *et al*, 1999) (140-144). The CVI was used in this study as it has the advantages of being easy to compute, easy to understand, focusing on both agreement of relevance among experts and consensus (proportion in agreement) rather than consistency (extent to which experts are consistent in their application of the rating scale), and providing both item and scale level information (135, 143, 145). The S-CVI value of 0.92 obtained is above the recommended standard of 0.8 for new scales. Furthermore, the majority of items had a modified kappa statistic that corresponded to either the 'good' or 'excellent' rating; only one item had 'fair' rating of 0.5. This suggests that agreement on relevance of each question was not due to chance and, overall, items were highly representative of the underlying construct.

For construct validity, the result of the one-way ANOVA with post-hoc analysis showed a statistically significant difference across the three groups. This result is in agreement with the underlying principle for the group comparison method for construct validity of a new instrument (137), and it therefore follows that the instrument may be useful in distinguishing between different levels of anticoagulation knowledge. The significant variation observed with some items after the individual item analysis further supports the difference in knowledge across the three groups. This may imply that these items would be useful in routine clinical practice as a quick approach in identifying patients with low levels of anticoagulation knowledge. The internal consistency and test-retest reliability coefficients were also acceptable. For the internal consistency reliability analysis, values of > 0.70 obtained across the three groups suggest that the items in the test are interrelated and of a reasonable length, and also measuring the same construct (138). Further, the result of the test-retest reliability showed correlation coefficients of 0.78 and 0.72 in the patient and pharmacist group, respectively. There has been some debate on the acceptable level for test-retest reliability due to varying statistical techniques, however, a recent systematic review

considered a minimum reliability threshold of 0.7 as being adequate (146). This suggests that the scale is expected to provide consistent scores over time in a stable population.

Participants in the patient group in the validation study scored a mean score of 62% on the AKT. This result is similar to those reported in prior studies. A mean score of 64% was recorded by Winans *et al* in inpatients new to warfarin therapy (147), while Tang *et al* reported a mean score of 48% in patients attending an anticoagulation clinic for at least 2 months (29). Similarly, Davis *et al* and Hu *et al* have also reported that less than 40% of patients in routine clinical practice have adequate anticoagulation knowledge (27, 148). These results suggest that there remains a significant gap in patient anticoagulation knowledge in contemporary practice, and further investigation in a larger cross-section of people taking oral anticoagulants is warranted.

Another important observation in the patient group is that participants taking the DOACs were less likely to view skipping a dose of their medication as a problem compare to participants taking warfarin. This is a critical knowledge gap because the DOACs have shorter half-lives compare to warfarin, and non-adherence to therapy even for a short period can result in loss of clinical effect and expose patients to significant risk (149). This suggests that significant attention should be given to the concept of medication adherence when designing and implementing an educational intervention in patients prescribed the DOACs.

3.6 Limitations

Among participants in the general public group, about 70% had formal education beyond high school level, including 28% with a post-graduate qualification. The high literacy level of this group may not be truly representative of the general public. However, the average score of this group was still significantly lower than both the patient and pharmacist groups. Also, participants in the three groups were not aged matched, and it is not known if a higher median age in the general

public group would have given a higher result. All the participants in the survey were given the opportunity of either completing the survey immediately upon receipt or returning it using a reply-paid envelope; we cannot rule out the possibility that some participants might have accessed additional resources despite being encouraged not to do so in the survey instructions. This may have increased the overall score in the survey. The relatively high score in the patient group may be as a result of the recruitment of confident and enthusiastic patients who have had or are undergoing some form of educational training on the use of oral anticoagulant medication, and may not necessary reflect the broader anticoagulant-medication taking population. For the test-retest reliability, not all the participants who completed the first test participated in the second test, and the impact of this on the test-retest reliability coefficient remains unknown. Lastly, the study was conducted in a single region, and the instrument may need to be validated in other regions globally.

3.7 Conclusion

To the best of our knowledge, the AKT is the first validated instrument that can be employed in assessing anticoagulation knowledge of patients taking either the VKAs or the DOACs. It appears to be a valid and reliable instrument in assessing different levels of anticoagulation knowledge. Therefore, it could be useful in routine clinical practice for determining gaps in patients' anticoagulation knowledge, measuring changes in anticoagulation knowledge over a period of time or in response to educational interventions, and in clinical research for determining the association between anticoagulation knowledge and health related outcomes.

CHAPTER FOUR

4.0 The relationship between knowledge, health literacy and adherence among patients taking oral anticoagulants for stroke thromboprophylaxis in atrial fibrillation

Overview

In this chapter, the Anticoagulation Knowledge Tool (AKT) was piloted in 48 patients with AF to investigate the relationships between oral anticoagulant knowledge, adherence and health literacy. This study was conducted to assess the usability of the AKT in a small sample using face-to-face interview. The results of the study showed that the AKT was able to detect OAC knowledge gaps in patients with AF, and suggest that knowledge, health literacy and medication adherence levels were suboptimal and positively related. This study was published in *Cardiovascular Therapeutics* (https://www.ncbi.nlm.nih.gov/pubmed/28869793) on September 26, 2017.

4.1 Abstract

Background: Patients' knowledge regarding their oral anticoagulant (OAC) treatment for stroke prevention in atrial fibrillation (AF), their level of medication adherence, and health literacy are known to affect treatment outcomes. However, contemporary data regarding the relationships between these variables are lacking.

Objective: To investigate the relationships between anticoagulant knowledge, health literacy, and self-reported adherence in patients taking warfarin and the directly acting oral anticoagulants.

Methods: A cross-sectional survey was conducted in 48 patients with AF identified from general practices. The Anticoagulation Knowledge Tool (AKT) was used to assess anticoagulation knowledge; the Short Test of Functional Health Literacy in Adults (s-TOFHLA) for health literacy; and the 8-item Morisky Medication Adherence Scale (MMAS) for medication adherence.

Results: Participants had mean scores of 61.6 ± 15.8, 7.2 ± 1.1, and 24.7 ± 9.5 for the AKT, MMAS-8 and s-TOFHLA, respectively. Significant correlations were observed between anticoagulation knowledge and health literacy with medication adherence (0.37, $P < .01$ and .30, $P < .05$, respectively). Participants with inadequate health literacy had a significantly lower mean knowledge score than those with adequate health literacy (55.8 ± 15.9 vs 66.1 ± 14.4, $P < .05$). Participants who self-reported adherence to their OAC had significantly higher knowledge scores than those who did not (67.5 ± 13.3 vs 56.1 ± 16.2, $P < .05$).

Conclusion: Significant correlations between health literacy, OAC knowledge, and adherence were observed, and these relationships should to be considered by health professionals responsible for monitoring patients who are prescribed anticoagulants. We also observed serious gaps in OAC

knowledge. Interventions designed to optimise the outcomes of anticoagulant treatment need to address these factors.

4.2 Introduction

Atrial fibrillation (AF) is associated with significant morbidity and mortality, and stroke resulting from AF presents a large and growing economic concern (150). Anticoagulation therapy in at risk patients with AF can markedly reduce stroke risk and is therefore an important component of AF management (150). Under-use of OACs in AF is often reported in terms of under-prescribing of treatment, but poor treatment outcomes in people with AF also commonly result from poor adherence or persistence with anticoagulant therapy even when it is prescribed, often with devastating consequences (28). Patients' oral anticoagulation knowledge, level of medication adherence and health literacy are known to affect treatment outcomes. However, contemporary data regarding the relationships between these variables are lacking.

Medication adherence in chronic disease is a worldwide problem. Up to 50% of patients are non-adherent to medications, including OACs (27, 151, 152). Limited health literacy is associated with poor warfarin and AF knowledge (153, 154). In addition, poor warfarin knowledge and lack of education about warfarin have been associated with inadequate anticoagulant control and increased haemorrhagic events, and those at highest risk of stroke have been shown to have the poorest knowledge regarding their treatment (68, 153, 155). It is unknown whether similar results will be seen in patients who take directly acting oral anticoagulants (DOACs).

The introduction of the DOACs has sought to address some of the pitfalls of warfarin therapy, however there are persisting challenges to overcome; adherence to the drug regimen being the most crucial. Due to their short half-lives, irregular or missed doses can increase the risk of stroke, as the patient will be inadequately anticoagulated during this time (156, 157).

The 2016 European Society of Cardiology (ESC) guidelines for the management of AF recommend an integrated approach to care with particular focus on the patient being central to effective management. Integral to patient-centred care is patient education, which in turn empowers self-management and shared decision making. As a European Heart Rhythm Association, priority research area and acknowledged by the ESC guidelines, more research is needed to determine the best way to deliver an integrated approach (150, 158).

Given the interest in integrated AF care, and the lack of contemporary data investigating the relationships between health literacy, adherence behaviours and medication knowledge of patients taking OACs for stroke thromboprophylaxis in AF, the aim of this study was to investigate the relationships between these variables and to assess the strength of the relationship between knowledge and health literacy.

4.3 Methods

4.3.1 Recruitment

Participants were recruited to the study from participating general practices or outpatient cardiologist clinics in Tasmania, Australia. Invitation letters with a response form were sent to the practices requesting their participation in the study and asking that patients with AF in their practices be given the opportunity to participate in the study. To be eligible to participate, participants had to be over 18 years of age, have a diagnosis of non-valvular AF, be currently taking warfarin or DOACs for stroke thromboprophylaxis and be able to provide informed consent. Participants were interviewed either at their regular GP surgery or in their home as these were considered familiar and comfortable surroundings. A $10 AUD shopping voucher was provided to all participants as recruitment incentive and as compensation for their time at the end of the interview.

4.3.2 Data collection

The interview consisted of four validated questionnaires - the 8-item Morisky Medication Adherence Scale (MMAS-8), Anticoagulant Knowledge Tool (AKT), Short Test of Functional Health Literacy in Adults (s-TOFHLA) and the Atrial Fibrillation Effect on Quality of Life (AFEQT) questionnaire, presented to participants in this order. Participants were introduced to the study using a script and all questionnaires were undertaken in an interview style, with the exception of s-TOHFLA which participants completed by themselves within a seven-minute time limit. Each interview took between 20 and 45 minutes and all were completed in a single session.

4.3.2.1 Adherence

To assess self-reported adherence behaviour, we used the MMAS-8 questionnaire, which asks seven dichotomous questions and one 5-point Likert scale question (159-161). The validated MMAS-8 was chosen as it has been shown to be a reliable predictor of adherence in patients taking medications for chronic diseases, such as antihypertensives, and has been used to assess adherence in those taking OACs (160, 162, 163). In assessing adherence using the MMAS-8, a score of 8 was considered adequate adherence, while a score of less than 8 was considered inadequate adherence (162).

4.3.2.2 Knowledge

To assess the level of knowledge of OAC therapy and its role, including participant perceptions/understanding of the risks and benefits, we used the AKT, which was developed to assess the anticoagulant knowledge of patients taking either warfarin or DOACs. A score of ‘1’ or ‘0’ was given for correct and incorrect answers, respectively. Participants taking a DOAC were required to answer only section ‘A’ with a total maximum score of 25 and participants taking

warfarin were required to answer sections ‘A’ and ‘B’ with a total maximum score of 35. Final scores were presented as percentages of correct answers for all participants (164).

4.3.2.3 Health Literacy

To assess functional health literacy, we used the s-TOFHLA (165). Dichotomous scoring of ‘1’ for correct answers and ‘0’ for incorrect answers was used and a maximum score of 36 could be achieved. In scoring the s-TOFHLA scale, a score of 23 and above was considered adequate health literacy, while a score of 22 and less was considered inadequate health literacy (153, 166).

4.3.2.4 Quality of Life

To assess AF specific health related quality of life we used the AFEQT. For AFEQT questions 1-20, responses were scored on a 1 to 7 Likert scale. An overall score of 0-100 could be achieved, corresponding to ‘complete disability’ to ‘no disability’, respectively. AFEQT was chosen as it combines the scores from four parameters: symptoms, daily activities, treatment concerns and satisfaction to a single measure with reliability, and has focused questions surrounding the use of anticoagulants (167, 168).

4.3.3 Statistical analysis

Statistical analysis was performed using SPSS version 24 (IBM, Armonk, New York, US). Means and standard deviations were used to summarise continuous variables, and independent sample t-tests were used for inferential statistics. s-TOFHLA and MMAS-8 scores were analysed as both continuous and dichotomous variables. Correlations between AKT, s-TOFHLA and MMAS-8 scores were determined using the Spearman rank coefficient. Logistic regression analysis was used to estimate regression coefficients for AKT and s-TOFHLA against MMAS-8 adherence scores in

both univariate and multivariate models. A *p* value of <0.05 was considered statistically significant for all analyses.

4.3.4 Sample size

Using a 5% margin of error and statistical power of 80%, we determined that a sample size of 40 participants would be sufficient to detect a moderate statistical correlation of 0.4 between the AKT score and s-TOFHLA score with the MMAS-8 adherence score.

4.3.5 Ethics

The Tasmanian Health and Medical Human Research Ethics Committee (reference number H0015395) approved this study. Informed consent was obtained from all individual participants included in the study.

4.4 Results

4.4.1 Demographic characteristics

Fifty participants were interviewed. The results of two participants were excluded because they had discontinued their OAC at the time of the interview, leaving data from 48 participants available for analysis. The average age of the participants was 76.4 ± 8.7 years and the majority (77.1%) were male (Table 15). Forty-two percent of participants had either high school education (Year 10 equivalent) or college (Year 12 equivalent) as the highest level of education completed. The majority of the participants were taking a DOAC (64.6%) at the time of the study, and had been taking an anticoagulant for greater than 2 years (75.0%).

Table 15. Demographic characteristics n (%)	
Parameter	**Overall Sample (n= 48)**
Male	37 (77.1)
Age in years (mean +/- SD)	76.4 ± 8.7
Highest education completed n (%)	
High school	14 (29.2)
College	6 (12.5)
Technical/ Vocational	13 (27.1)
Bachelor degree	11 (22.9)
Post graduate	4 (8.3)
Duration of anticoagulant therapy n (%)	
Less than 3 months	1 (2.1)
3-12 months	5 (10.4)
1-2 years	6 (12.5)
Greater than 2 years	36 (75.0)
Oral anticoagulant n (%)	
Warfarin	17 (35.4)
DOAC	31 (64.6)

4.4.2 Association between level of self-reported adherence and health literacy, knowledge and AF-related quality of life

Adequate adherence to the prescribed OAC was reported by 47.9% of participants and this group had a significantly higher total knowledge score than those who were non-adherent (67.5% vs 56.1%, $p = 0.011$) (Table 16). However, no association between the level of adherence with health literacy and AF-related quality of life was observed.

Table 16. Association between adherence level and study variables

Parameter	Overall Sample (n= 48)	Inadequate Adherence (MMAS-8 Score < 8) (n=25)	Adequate Adherence (MMAS-8 score = 8) (n=23)	p value
Total AKT score	61.6 ± 15.8	56.1 ± 16.2	67.5 ± 13.3	0.011*
s-TOFHLA	24.7 ± 9.5	22.9 ± 9.9	26.7 ± 8.8	0.171
Overall AFEQT	80.1 ± 15.8	81.3 ± 16.7	78.8 ± 14.9	0.593

*p <0.05

4.4.3 Level of health literacy and knowledge

As shown in Table 17, when participants were categorised based on their health literacy scores, those with inadequate health literacy had a significantly lower mean total anticoagulant knowledge score than those with adequate health literacy (55.8 ± 15.9 versus 66.1 ± 14.4, p = 0.02).

Furthermore, participants with inadequate health literacy were less likely than those with adequate health literacy to know why they had been prescribed an OAC (57.1% versus 85.2%, $p = 0.04$), less likely to know how the medication worked (42.9% versus 88.9%, $p = 0.001$) and less likely to be able to describe one sign of side effects to watch out for whilst taking an anticoagulant (28.6% versus 70.4%, $p = 0.03$). In addition, only 16.7% of all participants could mention three signs of side effects to watch out for while taking an OAC (Table 17).

Table 17. Anticoagulation knowledge score according to health literacy level				
Item	**Overall Sample (n= 48) n (%)**	**Inadequate Health Literacy (n=21) n (%)**	**Adequate Health Literacy (n=27) n (%)**	**p value**
What is the name of your anticoagulant medicine?	43 (89.6)	17 (81.0)	26 (96.3)	0.119
Why has your doctor prescribed you this medicine?	35 (72.9)	12 (57.1)	23 (85.2)	0.039*
How does this medicine work in your body?	33 (68.8)	9 (42.9)	24 (88.9)	0.001*
How many times a day do you need to take this medicine?	48 (100.0)	21 (100.0)	27 (100.0)	NA
For how long do you need to take this medicine (for example, 3 months, and 6 months, life-long)?	47 (97.9)	20 (95.2)	27 (100.0)	0.329
Why is it important to take this medicine exactly as your doctor has told you? (stroke)	28 (58.3)	10 (47.6)	18 (66.7)	0.192
Why is it important to take this medicine exactly as your doctor has told you? (bleeding)	1 (2.1)	1(4.8)	0 (0.0)	0.329
Is it important to take this medicine at the same time each day?	42 (87.5)	18 (85.7)	24 (88.9)	0.748

Is it okay to double the next dose of this medicine if you miss a dose?	46 (95.8)	21 (100.0)	25 (92.6)	0.161
Is it possible that skipping one dose of this medicine could worsen your condition?	19 (39.6)	7 (33.3)	12 (44.4)	0.446
Is it appropriate to stop taking this medicine once you feel better?	44 (91.7)	18 (85.7)	26 (96.3)	0.231
Is it safe to take anti-inflammatory medicines like ibuprofen (Nurofen® or Advil®) while you are taking this medicine?	28 (58.3)	15 (71.4)	13 (48.2)	0.105
Is it safe to take vitamin supplements and herbal medicines with this medicine without consulting your doctor?	30 (62.5)	15 (71.4)	15 (55.6)	0.264
Is there any benefit in taking more of this medicine than your doctor has told you to take?	44 (91.7)	18 (85.7)	26 (96.3)	0.231
Will drinking too much alcohol increase the risk of side effects with this medicine?	18 (37.5)	9 (42.9)	9 (33.3)	0.513
Is it necessary to inform a surgeon, dentist or other health professional that you are taking this medicine before undergoing surgery or a procedure?	47 (97.9)	20 (95.2)	27 (100.0)	0.329
Is it important that all the health care practitioners you see know that you are taking this medicine?	47 (97.9)	20 (95.2)	27 (100.0)	0.329
What is the most important side effect of this medicine?	21 (43.8)	7 (33.3)	14 (51.9)	0.208

THREE signs of side effects that you should watch out for while taking this medicine are: (1/3)	25 (52.1)	6 (28.6)	19 (70.4)	0.003*
THREE signs of side effects that you should watch out for while taking this medicine are: (2/3)	15 (31.3)	5 (23.8)	10 (37.0)	0.337
THREE signs of side effects that you should watch out for while taking this medicine are: (3/3)	8 (16.7)	2 (9.5)	6 (22.2)	0.231
THREE things you can do to reduce your risk of side effects are: (1/3)	16 (33.3)	4 (19.1)	12 (44.4)	0.059
THREE things you can do to reduce your risk of side effects are: (2/3)	7 (14.6)	1 (4.8)	6 (22.2)	0.072
THREE things you can do to reduce your risk of side effects are: (3/3)	6 (12.5)	1 (4.8)	5 (18.5)	0.133
What is the best step to take if you accidentally take too much of this medicine?	34 (70.8)	16 (76.2)	18 (66.7)	0.482
Warfarin specific questions				
Item	**Overall Sample (n=17)** **n %**	**Inadequate Literacy (n=9)** **n (%)**	**Adequate Literacy (n=8)** **n (%)**	**p value**
What is your target INR range?	11 (64.7)	5 (55.6)	6 (75.0)	0.431
What was your last INR reading?	16 (94.1)	8 (88.9)	8 (100.0)	0.347
Are routine INR tests necessary to know how well this medicine is working?	15 (88.2)	8 (88.9)	7 (87.5)	0.935

Is an INR value above your target range good for your general wellbeing?	13 (76.5)	6 (66.7)	7 (87.5)	0.334
Is it possible for INR values below your target range to be bad for your health?	12 (70.6)	5 (55.6)	7 (87.5)	0.161
Is it possible for what you eat to affect your warfarin therapy?	14 (82.4)	6 (66.7)	8 (100.0)	0.081
If you answered 'Yes' above, list THREE foods that can affect your anticoagulant therapy: (1/3)	12 (70.6)	5 (55.6)	7 (87.5)	0.161
If you answered 'Yes' above, list THREE foods that can affect your anticoagulant therapy: (2/3)	12 (70.6)	5 (55.6)	7 (87.5)	0.161
If you answered 'Yes' above, list THREE foods that can affect your anticoagulant therapy: (3/3)	11 (64.7)	4 (44.4)	7 (87.5)	0.066
List one vitamin that can significantly affect your anticoagulant therapy.	6 (35.3)	2 (22.2)	4 (50.0)	0.259
Total AKT score (%)	61.6 ± 15.8	55.8 ± 15.9	66.1 ± 14.4	0.022*

*p <0.05

4.4.4 Association between adherence, knowledge and health literacy

There were moderate positive correlations between the mean scores of self-reported adherence, anticoagulant knowledge and health literacy (figure 5). Multivariate analysis showed that anticoagulation knowledge was significantly associated with MMAS-8 score even after adjusting for health literacy score (OR, 1.050; 95% CI, 1.003 – 1.100; p = 0.036), Table 18). There were no statistically significant relationships between total AF specific health related quality of life scores and other study variables.

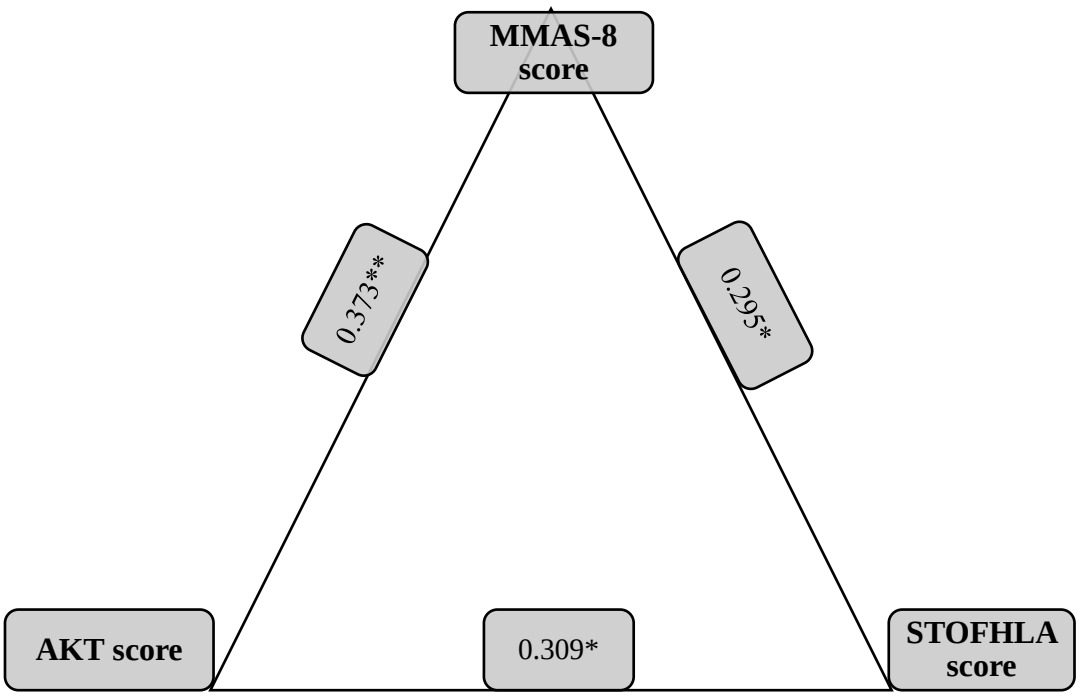

Figure 5: Correlations between study variables

*Correlation is significant at the 0.05 level (2-tailed)

** Correlation is significant at the 0.01 level (2-tailed)

Table 18. Association of knowledge and health literacy scores with MMAS-8 score (logistic regression)				
Independent variables	**Unadjusted model**		**Adjusted model**	
	OR (95%CI)	p value	OR (95%CI)	p value
Knowledge Score	1.054 (1.009 – 1.101)	0.017*	1.050 (1.003 – 1.100)	0.036*
Health Literacy Score	1.045 (0.981 – 1.114)	0.171	1.018 (0.948 – 1.092)	0.631
Model statistics: *Nagelkerke* R^2 = 18.1% CI, confidence interval; MMAS-8, 8-item Morisky medication adherence scale. * p <0.05				
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4.5 Discussion

This study provides valuable data supporting relationships between adherence, OAC knowledge and health literacy. Participants who self-reported adherence to their OAC had significantly higher knowledge scores than those who did not. In addition, participants with adequate health literacy achieved significantly higher knowledge scores. Positive correlations between health literacy, knowledge and adherence scores were also observed, suggesting that these concepts are interlinked and should be considered when managing patients taking OACs for stroke thromboprophylaxis in

AF. The Capability, Opportunity and Motivation (COM-B) model of Behaviour to increase medication adherence provides a dynamic framework in order to identify appropriate interventions that address the modifiable factors influencing non-adherence (33, 169). Mapping the results from this study to the COM-B framework suggests each of the domains (COM) are involved and need to be addressed in order to increase OAC adherence (B) (33, 169).

Poor adherence to OACs is frequently reported in the literature and has been associated with poor clinical outcomes (27, 28, 40, 102, 152). In our study, 48% of participants reported adequate adherence to their prescribed OAC. This is similar to the study by Davis *et al.* in patients taking warfarin, in which only 50% of participants reported adequate adherence (27). A recent review of adherence and persistence to OACs in AF found that in the studies available, poor adherence is associated with poor treatment outcomes such as stroke and bleeding (40). Yao *et al* recently undertook a large retrospective cohort study in patients taking OACs for stroke prevention in AF and found that those with a high estimated stroke risk were at an increased risk of stroke when they were not taking anticoagulation for 6 months or more (hazard ratio 2.73, $p < 0.001$), clearly indicating that better medication taking behaviour leads to better outcomes (28).

Taking into consideration the importance of adherence in ensuring a steady plasma concentration with DOACs and their lack of routine laboratory monitoring(157), our study suggests that patients taking DOACs may require routine follow up by health care practitioners (HCPs) to ensure that they adhere to their medication. This fit within the COM-B sub-category of Physical Opportunity, which suggests that HCP-patient communication and relationships can be improved through routine clinical follow up, in turn leading to increased adherence (33, 169).

We observed a total mean knowledge score of 62%. This is similar to the result of other studies in the literature, where a mean knowledge score of less than 70% has been reported in different

populations (46, 74, 164, 170). From the results of our study, participants who were considered adherent had a significantly higher mean total knowledge score than those who were non- adherent, and knowledge remained significantly associated with adherence even after adjusting for the level of health literacy. Forty percent of all participants did not know that taking an OACs as the doctor had prescribed reduced the risk of stroke and 60% of all participants did not know that skipping a dose of their OAC could worsen their condition. In support of these findings, a recent study by Desteghe *et al* found that 34% were unaware that AF could cause a stroke and 57% of the patients taking DOACs did not know what to do when they miss a dose (170). Lane *et al* found that only approximately 50% could name their condition and perceived it as a serious condition that could predispose them to a stroke (56). Few studies have examined whether poor DOAC knowledge leads to poor clinical outcomes, however this has been demonstrated in those taking warfarin (68, 153, 155). Our study reveals specific deficiencies in the knowledge of both warfarin and DOAC-taking participants. In addition, it provides a platform to inform the development of educational interventions and justifies the need for further research in this area.

Limited health literacy may be an indicator of deficits in warfarin knowledge (153, 154). Fang *et al* reported that 67% of patients taking warfarin for stroke prevention in AF had limited health literacy (s-TOFHLA score of 0-22) and this group had significantly inadequate disease and medication-related knowledge in comparison to those with adequate health literacy (153). These results align well with our study, which found that those with inadequate health literacy had a significantly lower mean total anticoagulant knowledge score in comparison to those with adequate health literacy. Participants with inadequate health literacy were less likely than those with adequate health literacy to know why they had been prescribed an OAC, less likely to know how the medication works and less likely to be able to describe one sign of side effects to watch out for while taking an anticoagulant. Patients need to know what they have been prescribed and

why, as well any possible side effects. Paucity in patients' knowledge can have a profound effect on the management of AF (171).

Lack of knowledge and health literacy, comprehension of the disease and treatment, perception of illness and beliefs about treatment including concern of side effects and bleeding fits within the COM-B sub-categories of Psychological Capability and Reflective Motivation (33, 169). It has been suggested that these categories can be addressed by HCPs giving information to patients to shape their knowledge, with the intention to enhance a patient's capability to understand and engage in their therapy (33, 169). With the goal of improving adherence through patient centred care, consideration of health literacy and its association with knowledge and adherence in patients taking OACs for stroke prevention in AF should therefore not be overlooked. Adherence may be improved through implementation of individually tailored educational interventions focusing on improving the disease and medication-related knowledge of the patient.

4.6 Limitations

There are a number of limitations to this study, including the cross-sectional methodology and small sample size. Furthermore, we did not collect information on the quality of education given to participants on their OACs upon initiation, nor did we determine if participants who were taking a DOAC at the time of the interview had previously been taking warfarin. The limitations of the tools used should also be considered. We anecdotally observed that many participants were unable to differentiate between the effect of AF and other co-morbidities such as heart failure or older age on quality of life. This made it difficult for participants to definitively say that AF was the condition causing their symptoms, such as shortness of breath or limiting their ability to exercise. Medication adherence was quantified by self-report; this approach can possibly overestimate the level of adherence observed (172).

4.7 Implications for further research

Recent clinical guidelines have placed emphasis on integrating the patient and their preferences into AF management to improve outcomes (150). The results of this study help to inform the implementation of patient centred integrated AF management and reinforce the need for additional research. Considering the demonstrated correlation between health literacy, knowledge and adherence, larger studies are required to determine if improving these patient centred aspects of OAC management in AF leads to improved treatment outcomes. Moreover, this study reveals gaps in the knowledge of participants taking OACs. A large prospective study assessing anticoagulant knowledge in this population will be useful in identifying specific areas of lacking knowledge to improve OAC education.

4.8 Conclusion

In conclusion, the results of this study demonstrate a significant relationship between health literacy, OAC knowledge and self-reported adherence behaviours. They also highlight inadequate medication adherence behaviour and health literacy levels, and gaps in patient oral anticoagulation knowledge. To adopt a true patient centred approach to AF management, it is important for HCPs to consider these variables in patients taking OACs for stroke prevention in AF. Interventions designed to optimise the outcomes of anticoagulant treatment need to address these factors.

CHAPTER FIVE

5.0 Anticoagulation knowledge in patients with atrial fibrillation: an Australian survey

Overview

This study aimed to address the third objective of this thesis. It focused on the use of the Anticoagulation Knowledge Tool to determine the level of oral anticoagulant knowledge in patients with AF, identifying domains where knowledge gaps exist, and assessing the association between patient-related factors and oral anticoagulant knowledge. The results from the pilot study reported in Chapter 4 suggested that OAC knowledge was suboptimal, and the AKT was able to provide reliable results using a traditional face-to-face interview approach. As such, the study reported in this chapter explored the use of an alternative approach, namely an online survey, to assess OAC knowledge in a larger, nationally representative sample of patients with AF. This paper was submitted to the *International Journal of Clinical Practice* in September 2017, and is currently under review.

5.1 Abstract

Background: Atrial fibrillation (AF) is the most commonly diagnosed arrhythmia in clinical practice, and is associated with a significant medical and economic burden. Anticoagulants reduce the risk of stroke and systemic embolism by approximately two-thirds compared to no therapy. Knowledge regarding anticoagulant therapy can influence treatment outcomes in patients with AF.

Objective: To measure the level of anticoagulation knowledge in patients with AF taking oral anticoagulants (OACs), investigate the association between patient-related factors and anticoagulation knowledge, and compare these results in patients taking warfarin and direct acting oral anticoagulant (DOACs).

Methods: Participants were recruited for an online survey via Facebook. Survey components included the Anticoagulation Knowledge Tool, the Perception of Anticoagulant Treatment Questionnaires (assessing treatment expectations, convenience and satisfaction), a modified Cancer Information Overload scale and the Morisky Medication Adherence Scale. Treatment groups were compared and predictors of OAC knowledge were identified.

Results: Participants taking warfarin had a higher knowledge score compared to those taking DOACs (n = 386, 73.4% ± 13.2% vs 65.7% ± 13.7%, p <0.001). Advancing age, type of OAC, health information overload and ease of OAC use (treatment expectation) were significant predictors of knowledge. Treatment expectation, including the belief that OAC treatment would cause bleeding side effects, varied significantly between participants taking warfarin and DOACs (p = 0.011).

Conclusion: The study identified knowledge gaps in patients taking OACs, and these deficiencies appeared to be greater in participants taking DOACs. Knowledge assessment should be integrated within patient counselling sessions to help identify and resolve knowledge deficits.

5.2 Introduction

Atrial fibrillation (AF) is the most commonly diagnosed arrhythmia in clinical practice, and is associated with a significant medical and economic burden (34). Patients with AF have a five-fold increase in their stroke risk (5); AF-related strokes are more severe and more likely to result in death compared to strokes in patients without AF (6, 7). Anticoagulants reduce the risk of stroke and systemic embolism by approximately two-thirds compared to no therapy irrespective of baseline risk (173) ; however, there are a number of factors that limit their optimal use (108, 174). It is well recognised that shared decision making with informed patients is important in the management of AF (36). Thus, patients need to be appropriately informed about their disease and treatment, including anticoagulant therapy.

Knowledge regarding anticoagulant therapy can influence treatment outcomes in patients with AF (29, 175). Patients with optimum knowledge regarding their medication and condition can participate in self-management and are more likely to adhere to prescribed medications, compared to those with inadequate knowledge (31, 176, 177). Various studies suggest that oral anticoagulant (OAC) therapy requires complex patient understanding for adequate self-management (27, 70, 174). Various patient-related factors including health information overload (178), treatment expectation (179), treatment convenience and satisfaction have been reported to be associated with knowledge regarding medication and therapy (180, 181). Health information overload has been investigated in patients with cancer (178); treatment expectation has been investigated in patients taking antibiotics (179); treatment convenience and satisfaction have been investigated in patients with hypertension and endocrine diseases (180, 181). These factors, however, have not been adequately studied in patients with AF.

In Australia, there has been an increasing rate of prescription of direct-acting oral anticoagulants (DOACs), as well as switching of patients previously taking warfarin to DOACs, since their approval and subsequent government subsidisation (32, 182, 183). The increased uptake of DOACs in clinical practice has also been corroborated by data from the United States, Canada, and the United Kingdom (184-187). Despite the increased uptake, most studies exploring OAC knowledge have been limited to participants taking vitamin K antagonists (VKAs), and have not involved patients taking DOACs (29, 50, 58, 59, 61, 147, 174, 188).

While DOACs have several advantages over warfarin, OAC therapy remains a high-risk treatment strategy (189). It is therefore important to be able to assess the adequacy of anticoagulation knowledge in patients prescribed either VKAs or DOACs and address any deficiencies or misconceptions. Therefore, this study aimed to (i) determine the level of anticoagulation knowledge in patients with AF taking oral anticoagulants (either warfarin or a DOAC), compare this level of knowledge between patients taking warfarin versus DOACs, and identify any domains where significant knowledge gaps exist; and (ii) investigate the association between treatment expectation, convenience and satisfaction, health information overload, and medication adherence with anticoagulation knowledge, and whether these factors differ for participants taking warfarin and DOACs.

5.3 Methods

5.3.1 Recruitment

Participants were recruited for an online survey (via LimeSurvey™) using Facebook. A Facebook page was created which contained the advertisement that was shown to users in their newsfeeds or on the right-hand advertising column of their Facebook page. A paid advertisement on Facebook targeted Australian residents over the age of 18 years. Potential survey participants were able to

click on the Facebook advertisement, from where they were directed to the LimeSurvey™ page containing an information page and the survey. A chance to enter into a drawing for an Apple iPad mini was used as an incentive to encourage participation. To maintain anonymity, prize draw details were not linked to survey responses. Participants were excluded from the analysis if they did not complete the survey, did not report having a diagnosis of AF, or did not report taking an OAC.

5.3.2 Survey

5.3.2.1 Recruitment

The survey requested participant demographic information including age, gender, postal code, annual income, highest educational level and employment status. Participants were then asked the name of the OAC they were taking, how long they had been taking it, and if they currently had a diagnosis of AF.

5.3.2.2 Anticoagulation Knowledge Tool

Anticoagulation knowledge was evaluated using the Anticoagulation Knowledge Tool (AKT), developed and validated in 2016 to assess the anticoagulation knowledge of patients taking either VKAs (warfarin) or DOACs (164). The AKT consists of two sections comprising general questions (section A - 20 items) and VKA-specific questions (section B - 8 items). All participants are required to answer the questions in section A, while only participants taking warfarin are required to answer the questions in section B. Participants taking DOACs can score a maximum of 25 points as they are only able to complete section A (164). Participants taking warfarin can score a maximum of 35 points as they need to complete both sections A and B (164). As per the

original design of the AKT, the present study reports final anticoagulation knowledge scores as percentages of answers correct, for all eligible participants.

5.3.2.3 Perception of Anticoagulant Treatment Questionnaire 1

Treatment expectation was evaluated using the validated Perception of Anticoagulant Treatment Questionnaire 1 (PACT-Q1) (190, 191) . The PACT-Q1 consists of seven items on a five-point Likert scale (1 = not at all, 5 = extremely), from which participants can select their response (190, 191). The PACT-Q1 scale has no global score. As such, each item was analysed individually.

5.3.2.4 Perception of Anticoagulant Treatment Questionnaire 2

Treatment convenience and satisfaction were evaluated using the validated Perception of Anticoagulant Treatment Questionnaire 2 (PACT-Q2). The PACT-Q2 consists of 20 items on a five point Likert scale. Of the 20 items, 13 items assessed treatment convenience, while seven items assessed treatment satisfaction. Global scores for both sections were calculated according to the original reports (190, 191).

5.3.2.5 Health information overload

Health information overload was assessed using a scale adapted from the Cancer Information Overload (CIO) scale (192). This scale, which has only been validated to predict colonoscopy screening, consists of eight items on a four-point Likert scale (1 = strongly disagree, 4 = strongly agree). The scale was adapted to assess the extent to which patients are overwhelmed by AF-related health information. The CIO scale was scored by summing the responses to all items, as in the original report (192).

5.3.2.6 Medication adherence

Medication adherence was assessed using the validated 8-item Morisky Medication Adherence Scale (MMAS-8) (160). Scores were calculated as stated in the original reports (159-161).

5.3.3 Sample size

The survey was active from February 2017 to May 2017. We estimated that a sample size of at least 384 was required to ensure that our results are generalizable to the Australian population, where the estimated prevalence of AF is 1-2% (8). This sample size calculation allowed for a 5% margin of error and a 95% confidence interval based on an estimated population of 460,000 people with AF (8). The recruitment period was open until a minimum of 384 eligible responses were obtained. Participants who did not have a diagnosis of AF or were not taking an OAC were considered ineligible.

5.3.4 Statistical analyses

Statistical analyses were conducted using SPSS version 23 (IBM, Armonk, New York, US). Sample means and standard deviations were used to summarise continuous variables, while proportions were used to summarise categorical variables. Independent sample t-tests and ANOVA were used for group comparison involving continuous variables, while the Mann-Whitney U test was used to compare the medians of ordinal variables. Chi-square tests were conducted to compare categorical variables. Linear regression analyses were used to identify the predictors of knowledge score in the univariate model, and variables with a p value of less than 0.1 were included in the multivariate model. (193-195). This p value was chosen because a less restrictive alpha value in the univariate analyses can identify a broad range of predictor variables that might be associated with the response variable (196). A p value of <0.05 was considered

statistically significant for all analyses. Standardised regression coefficients were determined to compare the association between predictor variables.

5.3.5 Ethics and consent

The Tasmanian Social Science Human Research Ethics Committee approved this study (reference number H0015972). Consent was implied by submission of the survey.

5.4 Results

A total of 924 responses to the online survey were received, of which 386 (41.8%) were complete and eligible for inclusion (figure 6). The mean cost of advertising through Facebook was $2.71 per response. The mean age of participants was 67.4 years (SD ± 7.9 years), and 68.4% were female (Table 19). Almost three-quarters were taking a DOAC, while a greater proportion of participants taking warfarin had been on the medication for more than 2 years than those taking a DOAC (84.0% vs 53.5%; $p < 0.0001$).

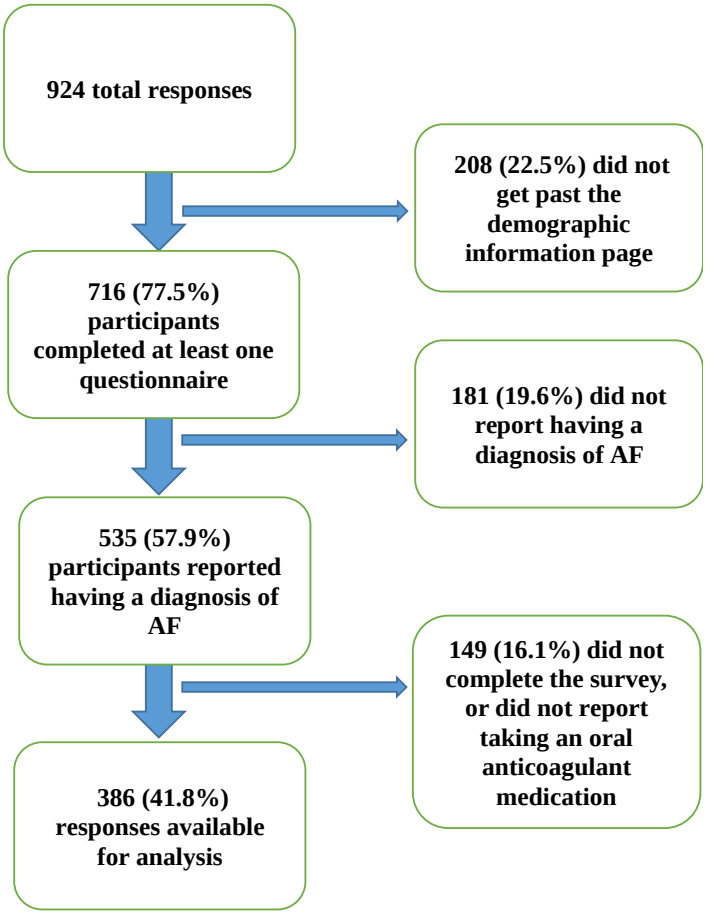

Figure 6: Flow chart of recruitment process

Table 19. Demographic information	
Characteristic	**Response (N=386)** **n (%)**
Sex	
Male	122 (31.6)
Female	264 (68.4)
Highest education completed	
Year 10 or below	138 (35.8)
Year 11 or 12	55 (14.2)
Certificate	52 (13.5)
Diploma	70 (18.1)
Bachelor's degree	41 (10.6)
Post graduate	25 (6.5)
Missing	5 (1.3)
Current employment status	
Not currently working	285 (73.8)
On leave (long-service)	7 (1.8)
Casual work	19 (4.9)
Part-time work	34 (8.8)
Full-time work	41 (10.6)
Annual income range	
0 – $18,200	104 (26.9)
$18,201 – $37,000	113 (29.3)

$37,001 – $80,000	70 (18.1)
$80,001 and greater	39 (10.1)
Prefer not to say	60 (15.5)
Duration of anticoagulant therapy	
Less than 3 months	25 (6.5)
3-12 months	44 (11.4)
1-2 years	80 (20.7)
Greater than 2 years	237 (61.4)
Oral anticoagulant	
Warfarin	100 (25.9)
Rivaroxaban	123 (31.9)
Apixaban	121 (31.3)
Dabigatran	42 (10.9)

Participants taking warfarin had a higher overall knowledge score compared to those taking a DOAC (73.4% vs 65.7%; $p < 0.0001$). On analysis of section A (the general questions), warfarin users still had a significantly higher knowledge score than DOAC users (71.6% versus 65.7%; $p < 0.0001$). No significant difference was observed for any of the items in the knowledge test between participants taking different DOACs. Of all participants, 5.9% of participants could identify three things they could do to reduce the risk of adverse effects, 23.8% could list three signs of side effects to look out for, 26.4% agreed that skipping a dose of their medication could have a negative consequence on their health, and 65.5% knew that the most important adverse effect of OAC therapy is bleeding.

Items on the knowledge test answered correctly by a significantly different proportion of participants taking warfarin to those taking the DOACs are shown in Table 20.

Table 20. Items from the knowledge test with significant variation between participants taking warfarin and DOACs

Item (AKT)	Warfarin (N=100) n (%) correct	DOACs (N=286) n (%) correct	p value
For how long do you need to take this medicine (for example, 3 months, and 6 months, life-long)?	99 (99.0)	273 (94.5)	0.026
Why is it important to take this medicine exactly as your doctor has told you? (bleeding)[a]	22 (22.0)	14 (4.9)	<0.001
Is it important to take this medicine at the same time each day?	93 (93.0)	224 (78.3)	<0.001
Is it safe to take vitamin supplements and herbal medicines with this medicine without consulting your doctor?	77 (77.0)	182 (63.6)	0.009
Will drinking too much alcohol increase the risk of side effects with this medicine?	66 (66.0)	121 (42.3)	<0.001
What is the most important side effect of this medicine?	75 (75.0)	178 (62.2)	0.015
THREE things you can do to reduce your risk of side effects are: (two)[b]	34 (34.0)	55 (19.3)	0.005
Total knowledge score (% ± SD)	73.4 ± 13.2	65.7 ± 13.7	<0.001

[a] Number of participants who could mention 'to minimise the risk of bleeding.'

[b] Number of participants who could mention two things they could do to reduce the risk of side effects.

Treatment expectations are shown in Table 21. Compared to those taking DOACs, participants taking warfarin had a significantly higher median score on the PACT-Q1 scale regarding (i)

confidence in the prevention of blood clot by OACs, (ii) expectation of bleeding side effects, and (iii) concerns about making a mistake when taking OACs (Table 21: items A1, A3, and A5). Conversely, those taking DOACs had a higher median score regarding (i) OAC that is easy to use, (ii) self-management of therapy, and (iii) concern regarding cost of therapy (Table 21: items A4, A6, and A7).

Table 21. Comparison of treatment expectations between participants taking warfarin and the DOACs

Items (PACTQ-1)	**Warfarin median (IQR)**	**DOACs median (IQR)**	**p value**
A1. How confident are you that your anticoagulant treatment will prevent blood clots?	4 (4-5)	4 (3-4)	0.040
A2. Do you expect that your anticoagulant treatment will relieve some of the symptoms you experience?	2 (1-3)	2 (1-3)	0.691
A3. Do you expect that your anticoagulant treatment will cause side effects such as minor bruises or bleeding?	4 (3-4)	3 (2-4)	0.011
A4. How important is it for you to have an anticoagulant treatment that is easy to take?	4 (4-5)	5 (4-5)	0.008
A5. How concerned are you about making mistakes when taking your anticoagulant treatment?	2 (1-3)	1 (1-2)	0.002
A6. How important is it for you to take care of your anticoagulant treatment by yourself?	4 (4-5)	5 (4-5)	0.042
A7. How concerned are you about how much you may have to pay for your anticoagulant treatment?	1.5 (1-3)	2 (1-4)	0.044
1= not at all, 5= extremely			

The mean scores for treatment convenience and satisfaction were 88.4% ± 10.34 and 68.6% ± 14.51, respectively. (ii) The mean scores for health information overload was 16.8 ± 3.95 (out of a possible score of 32) and 7.2 ± 1.14 (out of a possible score of 8) for medication adherence. No significant differences were observed between participants taking warfarin and DOACs for each of these variables.

In multivariate analysis, age, type of OAC, health information overload score, and ease of use (PACT-Q1) were significant independent predictors of knowledge. The standardised regression coefficients showed that type of OAC and information overload had the largest effect on OAC knowledge (-0.245 and -0.189, respectively) (Table 22). The analysis showed that the predictors explained 15.0% of the variance in knowledge score ($R^2=0.15$, $F(10, 374) = 7.76$, $p < 0.0001$) (Table 22).

Table 22. Predictors of anticoagulation knowledge score (multivariate analysis)			
Independent variables	**B (95% CI)**	**β (95% CI)**	**p value**
Age (years)	-0.226 (-0.396 – -0.056)	-0.128 (-0.221 – -0.035)	0.009*
Gender (male)	-2.757 (-5.595 – -0.081)	-0.092 (-0.183 – 0.002)	0.057
Education (> year 12)	1.344 (-1.387 – 4.074)	0.048 (-0.050 – 0.142)	0.344
Duration of oral anticoagulant therapy (> 2 years)	1.651 (-1.135 – 4.438)	0.058 (-0.036 – 0.155)	0.245
Type of oral anticoagulant (DOACs)	-7.793 (-10.942 – -4.645)	-0.245 (-0.340 – -0.153)	<0.001*
Cancer Information overload scale	-0.666 (-1.014 – -0.318)	-0.189 (-0.283 – -0.094)	<0.001*
A1. How confident are you that your anticoagulant treatment will prevent blood clots?	1.113 (-0.543 – 2.770)	0.066 (-0.031 – 0.161)	0.187
A3. Do you expect that your anticoagulant treatment will cause side effects such as minor bruises or bleeding?	0.950 (-0.167 – 2.066)	0.080 (-0.015 – 0.169)	0.095
A4. How important is it for you to have an anticoagulant treatment that is easy to take?	2.278 (0.791 – 3.766)	0.153 (0.060 – 0.253)	0.003*
A6. How important is it for you to take care of your anticoagulant treatment by yourself?	-0.048 (-1.463 – 1.367)	-0.003 (-0.103 – 0.093)	0.947

B = Unstandardised regression coefficient, **β** = Standardised regression coefficient, CI = confidence interval

*Significant independent predictors.

5.5 Discussion and conclusion

5.5.1 Discussion

We have described the result of a national survey on anticoagulation knowledge involving 386 participants with AF taking OACs. While studies have been conducted to investigate anticoagulation knowledge in several countries (27, 29, 50, 54, 57, 58, 61, 66, 69, 147, 148), most of these studies have either not provided information regarding the validity of the instrument used in assessing anticoagulation knowledge (27, 29, 57, 58, 66, 69), or have focused solely on the VKAs (50, 61, 147). The present study presents a unique approach as it uses a scale that has been validated in the Australian population and included participants taking warfarin and the DOACs.

Overall, knowledge gaps were observed in key areas of self-management including missing a dose, drug interactions, recognising bleeding as an important side effect, actions to reduce the risk of side effects and the effect of excessive alcohol consumption. These findings are similar with those of other studies across several populations in which suboptimal OAC knowledge has been consistently reported (27, 29, 50, 54, 57, 58, 61, 66, 69, 147, 148). However, to our knowledge, this is the first study to compare OAC knowledge between patients taking warfarin and DOACs. This is important because of the intrinsic differences in self-management of DOACs compare to warfarin therapy, especially the non-requirement for routine coagulation monitoring and shorter half-lives of the DOACs.

Participants taking warfarin had a significantly higher knowledge score in both the general questions and the overall test than those taking DOACs. There are several potential explanations for this finding. Patients taking warfarin may have received more intensive counselling, especially if dose modification was required after an international normalised ratio (INR) test. Conversely, due to the relative simplicity of DOAC therapy, DOAC users could have had less frequent interactions with health care practitioners (HCPs). The number and quality of patient-HCP interactions has been reported as a determinant of medication knowledge (197-199); the number of patient-HCP interactions is perceivably higher in warfarin users compared to DOAC users given the requirement for frequent INR monitoring. However, we did not capture the number of counselling interactions or the quality of education participants had received. Furthermore, the standardised regression coefficients showed that taking a DOAC was negatively associated with knowledge, and had the largest effect on knowledge scores. This further confirms the lower knowledge level observed in participants taking DOACs.

The influence of age on OAC knowledge level has been investigated in diverse settings, and advancing age has been identified as negatively correlated with OAC knowledge in several studies. Joshua *et al* (54) and Nadar *et al* (59) have reported lower knowledge levels in patients older than 60 and 61 years, respectively. Various other studies (56, 60-64) have found that advancing age is negatively associated with OAC knowledge. Thus, our finding aligns with the wider literature.

The association between information overload and knowledge may be mediated by individual differences in health literacy levels and information-seeking behaviours. In a United States study involving patients taking warfarin through an anticoagulation clinic, limited health literacy was strongly associated with poor OAC knowledge, even after adjusting for age, sex, ethnicity, education and duration of OAC therapy (174). While there are not any studies examining health

information overload in patients with AF, there is research to suggest that health information overload is a probable cause of decline in information-seeking behaviour of breast cancer survivors (200). The authors suggested that the decline could be because survivors were overwhelmed and frustrated by the amount of information they encountered (200). Consequently, patients with limited health literacy and poor information-seeking behaviour would be more likely to have suboptimal knowledge. The importance of having an OAC that is easy to take was positively associated with OAC knowledge level. This could be because patients with greater knowledge genuinely understand the complexity of OAC therapy and therefore value a hassle-free treatment option.

The comparison of treatment expectation between participants taking warfarin and DOACs showed that those taking warfarin were more confident that their OAC would prevent blood clots compare to those taking the DOACs. This could be related to the typically longer treatment duration among patients taking warfarin. Participants taking warfarin, however, had a greater expectation that their OAC would cause bleeding side effects and were more concerned about making mistakes when taking their OAC therapy. This could be due to the receipt of more comprehensive medication counselling regarding the complexities and risks of warfarin therapy, reinforced by the requirement for routine INR monitoring and the prescription of varying doses of warfarin in accordance with their INR results (2).

Participants taking DOACs attached a greater importance to having an OAC that is easy to use and self-manage. If these patients were actively involved in the prescribing decision about their OAC, as dictated by best practice guidelines (34), this could be the reason why they were prescribed a DOAC by their physician. However, participants taking DOACs were more concerned about the cost of their medication, perhaps related to the younger demographic of respondents based on the

recruitment strategy employed. These findings highlight that patients' preferences should be considered among other factors when initiating and continuing OAC treatment in AF.

Further research is required to identify reasons for the lower knowledge scores in participants taking the DOACs, and the impact of counselling and education intervention on the knowledge level of patients prescribed OAC in general. We also need to better understand treatment expectations and the burden of health information experienced by patients taking OAC and the impact of these factors on other patient-related outcomes, including anticoagulation knowledge.

The study is not without some potential limitations. As is common with online surveys, participants may have accessed other sources while providing responses (201), which may have influenced the results obtained. In addition, recruiting through Facebook may have led to the sampling of a selected population that may not fully represent the target population, and the inclusion of only confident and enthusiastic respondents. There is increasing evidence, however, that Facebook is a useful tool for recruiting older patients aged 65 years and above. Greenwood *et al*, reported that of all online adults, 62% of those aged 65 years and older used Facebook (202). A recent study by Cowie *et al* also reported that Facebook is a useful tool for enrolling older participants into clinical trial (203). The CIO scale, although validated to predict colonoscopy screening, is yet to be validated in patients with AF. Lastly, since the study was designed as a self-reported online survey, it was not possible to verify the accuracy of respondents' diagnosis, clinical, and demographic characteristics. Our study was strengthened by the use of a knowledge scale pre-validated in the same population (164), and a large sample size to ensure the results are generalisable to Australian residents with AF.

5.5.2 Conclusion

This study identified significant knowledge gaps in patients with AF taking OACs, and these deficiencies appear to be greater in participants taking the DOACs. Type of OAC, health information overload, advancing age, and patients' perceptions regarding the ease of use of OAC were significantly associated with OAC knowledge. Lastly, treatment expectations varied between participants taking warfarin and DOACs. These findings may increase understanding of patient-related factors that can influence treatment outcome in OAC therapy.

5.5.3 Practice implications

Patients with adequate anticoagulation knowledge can better participate in shared-decision making and self-management of their condition. We have demonstrated that OAC knowledge is suboptimal in the Australia setting, with even lower knowledge levels among patients taking DOACs. Knowledge assessment should be integrated within counselling sessions, and be provided to patients at initiation of OAC therapy and periodically thereafter, to identify and address knowledge gaps. In the absence of routine anticoagulation monitoring for DOACs, a similar follow-up program should be implemented for DOAC users to assess OAC knowledge and other patient-related outcomes. Treatment expectations of patients should also be assessed prior to commencement of therapy, as this would help guide the choice of OAC. These approaches would potentially improve self-management and subsequently positively influence treatment outcomes.

CHAPTER SIX

6.0 Adherence to oral anticoagulants in atrial fibrillation: an Australian survey

Overview

This study aimed to address the fourth objective of this thesis. It focused on estimating the proportion of patients who are non-adherent to oral anticoagulants, identifying predictors of adherence, and determining if patient-related factors vary across levels of adherence in patients with atrial fibrillation. The results from the pilot study reported in Chapter 4 suggested that OAC adherence was suboptimal in patients with AF. As such, the present study further investigated the extent of OAC non-adherence and identified relevant predictors in a nationally representative sample. Moreover, the present study explored factors related to each of the three components of the Capability, Opportunity and Motivation Model of Behaviour (COM-B) as they have been previously reported to influence OAC adherence. This study was a secondary analysis of data from the previous knowledge survey. This paper was submitted to the *Cardiovascular Drugs and Therapy* in December 2017, and is currently under review.

6.1 Abstract

Objective: Oral anticoagulant (OAC) therapy is highly effective for stroke prevention in patients with atrial fibrillation (AF). However, optimal adherence is essential to ensure its efficacy and safety. The aim of this study was to investigate the proportion of patients who are non-adherent to OAC, identify the predictors of adherence, and determine if patient-related factors vary across adherence levels in Australia.

Methods: Respondents were recruited for an online survey using Facebook. Survey instruments included the Morisky Medication Adherence Scale, the Anticoagulation Knowledge Tool, the Perception of Anticoagulant Treatment Questionnaires, and a modified Cancer Information Overload scale. Predictors of medication adherence were identified using ordinal regression analysis.

Results: Of the 386 responses eligible for analysis, only 54.9% reported a high level of adherence. Participants aged 65 years or younger were less likely to have high adherence compared to older participants (OR, 0.54; 95% CI, 0.33 – 0.88; p = 0.013), while females were more likely to be highly adherent compared to males (OR, 1.69; 95% CI, 1.08 – 2.64; p = 0.023). The ordinal regression analysis showed that age, gender, treatment satisfaction, information overload, concerns about making mistake when taking OACs and cost of medication were significant predictors of adherence.

Conclusion: Self-reported non-adherence to OAC is common among patients with AF. A focus on supporting people who are at higher risk of non-adherence is needed to maximise the benefit of OAC therapy in this population.

6.2 Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, and is responsible for 20-30% of all strokes (34). Oral anticoagulant (OAC) therapy is highly effective for stroke prevention in patients with AF (204). Evidence from clinical trials demonstrates that both warfarin (205) and the direct oral anticoagulants (DOACs) (26) reduce the risk of stroke by 64% to 70% (206). However, optimal adherence is essential to ensure both efficacy and safety with OAC therapy (40).

Studies have reported that more than 40% of patients with AF are non-adherent to OAC therapy (27, 106). Patients who adhere to OAC therapy are less likely to suffer stroke or major bleeding compared to those who do not (28, 30). As a result, experts have recently recommended a structured follow-up programme for all anticoagulated AF patients to improve adherence and persistence to OAC therapy (207).

Various studies have investigated adherence issues surrounding warfarin usage (27, 30). Warfarin use is challenging in clinical practice due to the requirement for routine blood monitoring, and numerous food and drug interactions (18); these factors often impose lifestyle changes on the patient (18, 208). They can lead to non-adherence, instability of anticoagulation control, as well as discontinuation of therapy (208). Consequently, poor adherence to warfarin therapy has been associated with increases in the rate of both bleeding and embolic events (30).

While international normalised ratio monitoring can be useful in identifying non-adherent warfarin patients, identifying non-adherent DOAC patients is more challenging in the absence of a similar test (209). Additionally, compared to warfarin, it has been suggested that even a short period of medication non-adherence to DOACs could result in a catastrophic loss of clinical effect (18).

Patient-related factors such as knowledge (59), health information overload (210), treatment convenience and satisfaction (211) have been investigated in patients with cardiovascular diseases. However, little is known about variation in patient-reported factors with regards to adherence in patients with AF. Consequently, we aimed to (i) estimate the proportion of patients who are non-adherent to OAC and identify predictors of adherence, and (ii) determine if patient-related factors vary across levels of adherence in patients with AF.

6.3 Methods

This study was a secondary analysis of an Australian OAC knowledge survey in patients with AF, in which respondents were recruited online (via LimeSurvey™) using Facebook. The survey requested socio-demographic characteristics including age, gender, level of education, annual income and type of employment. The survey also requested the type of OAC respondents were taking and the duration of therapy.

6.3.1 Survey instruments and scoring

Survey instruments used included the Morisky Medication Adherence Scale (MMAS-8) (159-161) to assess levels of adherence (low, medium and high); the Anticoagulation Knowledge Tool (AKT) to assess OAC knowledge (164); the Perception of Anticoagulant Treatment Questionnaires (PACT-Q1 and PACT-Q2) to assess treatment expectations, convenience and satisfaction (190, 191); and the modified Cancer Information Overload (CIO) scale to assess health information overload (192). The CIO scale was modified by replacing the word 'cancer' with 'atrial fibrillation' to suit patients with AF.

The MMAS-8 consist of eight items and was scored according to the information in the original reports (159-161). The AKT consists of two parts with 20 general items and eight items related to

vitamin K antagonists (VKAs), respectively. In addition to the general questions, participants taking warfarin are also required to answer the VKA-specific items. Final knowledge scores were presented as percentages in accordance with the original report (164). The PACT-Q1 scale assessing treatment expectation comprises seven items on a five-point Likert scale (1 = not at all, 5 = extremely) and has no global score; as such, each item was scored individually (190, 191). The PACT-Q2 assessing treatment convenience and satisfaction consists of 20 items on a five-point Likert scale. Global convenience and satisfaction scores were calculated according to the procedure in the original reports (190, 191). The CIO scale was scored by summing the responses to all eight items, as in the original report (192).

6.3.2 Recruitment and sample size

The survey targeted Australian residents with AF who were taking an oral anticoagulant. A paid advertisement on Facebook targeted adults over the age of 18 years. We estimated that a sample size of 384 Australians with AF was sufficient to make the results generalisable to the broader Australian population of people with AF considering an estimated prevalence of 1-2% (8). The sample size estimation was based on a calculation used for prevalence studies (212), considered a 5% margin of error and a 95% confidence interval. Screening questions were included in the survey to exclude respondents who did not have a diagnosis of AF or were not currently taking an OAC.

6.3.3 Statistical analyses

Analyses were conducted using SPSS version 23 (IBM, Armonk, New York, US). Continuous variables were reported as means and standard deviations, while categorical variables were reported as proportions. ANOVA was used to compare study variables across the levels of adherence, while predictors of medication adherence were identified using ordinal regression analyses. Ordinal regression analysis was chosen to model the three levels of adherence

simultaneously, while considering the ordered relationship between them (213). The maximum number of variables to be included in the multivariate analysis was determined using the *50+ 8k* rule (214), where *k* represents the number of predictors (214). Variables with a p value of less than 0.1 in the univariate analyses were considered eligible for the multivariate analysis (196), and a p value of less than 0.05 was considered statistically significant for all analyses.

6.3.4 Ethics and consent

The Tasmanian Social Science Human Research Ethics Committee (reference number H0015972) granted ethical approval for the research. Consent was implied by submission of the survey.

6.4 Results

There were a total of 924 respondents to the survey, and 386 (41.8%) participants reported taking an OAC for AF, and completed the survey. The mean age of respondents was 67.4 years (SD ± 7.9 years), of whom 69% were aged 65 years or older; 74.1% were taking a DOAC. A total of 212 respondents (54.9%) reported high adherence (Table 23). There were statistically significant associations between current employment and gender and adherence. Of note, females had a significantly higher score on two items on the MMAS-8 measuring unintentional non-adherence: 'Do you ever forget to take your medicine?' (0.81 versus 0.71; p = 0.04), and 'How often do you have difficulty remembering to take your medicine?' (0.93 versus 0.89; p = 0.02). No significant difference in adherence was observed between patients taking warfarin and DOACs. Respondents were evenly distributed based on Socio-Economic Indexes for Areas (SEIFA), an index that ranks areas in Australia based on relative socioeconomic characteristics (215).

Table 23. Demographic information				
	Low Adherence (MMAS <6) (n=54)	**Medium Adherence (MMAS 6 to <8) (n=120)**	**High Adherence (MMAS 8) (n=212)**	**p value**
Gender				
Female	28 (51.9)	81 (67.5)	154 (72.6)	0.014
Male	26 (48.1)	39 (32.5)	58 (27.4)	
Education [a]				
Year 12 and below	27 (50.0)	53 (44.2)	113 (53.3)	0.108
Greater than year 12	27 (50.0)	63 (52.5)	98 (48.7)	
Missing	0 (0.0)	4 (3.3)	1 (1.3)	
Employment				
Not currently working	36 (66.7)	79 (65.8)	170 (80.2)	0.007
Currently working	18 (33.3)	41 (34.2)	42 (19.8)	
SEIFA				
Decile 1-5	26 (48.1)	62 (52.1)	105 (49.8)	0.870
Decile 6-10	28 (51.9)	57 (47.9)	106 (50.2)	
Duration of therapy				
<2 years	23 (42.6)	52 (43.3)	74 (34.9)	0.257
>2 years	31 (57.4)	68 (56.7)	138 (65.1)	
Type of oral anticoagulant				
Warfarin	15 (27.8)	25 (20.8)	60 (28.3)	0.620
Apixaban	15 (27.8)	39 (32.5)	67 (31.6)	
Rivaroxaban	17 (31.5)	45 (37.5)	61 (28.8)	
Dabigatran	7 (13.0)	11 (9.2)	24 (11.3)	
SEIFA, Socio-Economic Indexes for Areas [a] 'Missing' was excluded from the analysis.				

Although no significant difference in knowledge scores was observed across the three adherence levels, treatment convenience and satisfaction scores were significantly greater in the high adherence group than both the low and medium adherence groups (Table 24). Participants who reported high adherence also had a significantly lower information overload score than both the low and medium adherence groups.

Table 24. Association between adherence levels and patient-related factors

Parameter	Low Adherence (MMAS< 6) (n=54)	Medium Adherence (MMAS 6 to <8) (n=120)	High Adherence (MMAS 8) (n=212)	p value
Knowledge score	66.3 ± 13.8	66.2 ± 13.7	69.0 ± 14.0	0.169
Convenience score	83.7 ± 11.4	85.9 ± 12.7	91.0 ± 7.5	<0.001
Satisfaction score	58.9 ± 15.7	65.8 ± 13.9	72.6 ± 13.0	<0.001
Information overload scale	18.1 ± 4.2	17.7 ± 3.6	16.0 ± 3.9	<0.001

The ordinal regression analysis showed that age, gender, treatment satisfaction, information overload, concerns about making mistake when taking OACs and cost of medication were significant predictors of adherence (Table 25). The model indicated that females were almost twice as likely to be adherent as males (OR, 1.7; 95% CI, 1.1 – 2.6; p = 0.02), while patients aged 65 or younger were less likely to be adherent to OAC than older patients (OR, 0.5; 95% CI, 0.3 – 0.9;

p = 0.01). The predictors included in the multivariate model explained 29.8% of the variation in adherence (*Nagelkerke* R^2=0.298; χ^2 = 113.76, p <0.001).

Table 25. Multivariate ordinal logistic model of factors associated with high adherence to oral anticoagulants		
Characteristics	**Odds ratio (95%CI)**	**p value**
Age (≤ 65 years)	0.54 (0.33 – 0.88)	0.013
Gender (female)	1.69 (1.08 - 2.63)	0.023
Employment (not working)	1.41 (0.85 – 2.36)	0.187
Knowledge score	1.01 (1.00 – 1.03)	0.180
Satisfaction score	1.04 (1.02 – 1.06)	<0.001
Convenience score	1.00 (0.98 – 1.02)	0.954
Information overload score	0.94 (0.89 – 1.00)	0.048
A1. How confident are you that your anticoagulant treatment will prevent blood clots?	1.11 (0.15 – 1.47)	0.497
A2. Do you expect that your anticoagulant treatment will relieve some of the symptoms you experience?	1.06 (0.89 – 1.27)	0.521
A5. How concerned are you about making mistakes when taking your anticoagulant treatment?	0.69 (0.57 – 0.83)	<0.001
A6. How important is it for you to take care of your anticoagulant treatment by yourself?	1.11 (0.90 – 1.38)	0.334
A7. How concerned are you about how much you may have to pay for your anticoagulant treatment?	0.84 (0.72 – 0.97)	0.020
Nagelkerke R^2 = 29.8 %		

6.5 Discussion

Approximately 50% of respondents reported low or medium adherence to OACs in this study, which highlights the need to support OAC adherence among Australian patients with AF. Specifically, patients who are aged ≤65 years, dissatisfied with their therapy, with higher perception of information overload, and concerned about making mistakes with taking OAC or the cost of their medications should be targeted for support and education.

The present study has some limitations. The use of self-reported adherence has been associated with overestimated adherence levels (93); however the MMAS-8 has been validated in several populations (216). Recruiting online may have also led to the inclusion of patients not adequately representative of the broader population of patients with AF. Although studies have found demographic and baseline characteristics to be comparable in respondents recruited online and face-to-face, online respondents tend to be significantly younger (217). As a result, this study may have focused more on younger patients with AF. In addition, the survey design required only patients taking OAC to participate. This may have resulted in the exclusion of patients with AF who had discontinued OAC therapy altogether. Despite the potential limitations, our study is strengthened by the inclusion of participants taking warfarin and DOACs, therefore capturing responses from participants taking a spectrum of OAC medications used in clinical practice. Additionally, given the large sample size, and the recruitment of participants nationally, our findings may be applicable to a wider population of Australian adults with AF. While many online studies have reported respondents to be largely from a higher socioeconomic background (218), in the present study an even distribution of participants was observed based on socioeconomic characteristics. This further suggests the sample was representative of the broader population.

The relationship between age and adherence has been investigated in patients with cardiovascular diseases (131, 219, 220). Although different study designs and age group classifications have been employed, the available evidence suggests that younger patients are more likely to be non-adherent to prescribed medication (131). This is consistent with our finding that patients aged 65 years and younger were more likely to be non-adherent to OAC. The reason for better adherence in older patients could be related to the presence of multiple comorbidities, thereby making older patients more concerned about their health, leading to better medication-taking behaviour (131). Since non-adherence to OAC is a significant concern in AF management, more emphasis should be placed on younger patients, as they may require additional support with managing their medication.

The relationship between gender and adherence to medication is inconsistent. Some studies have reported females to have better adherence to prescribed medication (221, 222), while other studies have reported the contrary (223, 224). In addition, some studies have not reported any association between gender and adherence levels (225, 226). The lower adherence in males in the present study could be attributed to their responses on two questions related to unintentional non-adherence; this suggests unintentional non-adherence is the likely cause of lower adherence in males. In clinical practice, collaborative efforts should be made by healthcare workers to understand if patients' non-adherence behaviour is intentional or unintentional. This would assist in the development of appropriate strategies for improving medication-taking behaviour. For example, reminders and pill organisers, among other strategies, may be beneficial in resolving unintentional non-adherence (227).

Although satisfaction with treatment was a significant predictor of adherence in the multivariate analysis, treatment convenience was not. This suggests that how reassured patients felt after taking an OAC is a more important determinant of adherence than difficulty experienced with OAC

therapy. This is further supported by the similar adherence levels observed between respondents taking warfarin, and the more convenient DOAC therapy (228). While satisfaction has been consistently associated with adherence in both cardiovascular and non-cardiovascular diseases (229), one study in patients taking warfarin has reported no association, although the number of warfarin users who were adherent was very low (230). The positive association observed in the present study is consistent with the broader literature. Therefore, efforts should be made to evaluate patients' satisfaction with OAC therapy in routine practice and interventions to improve satisfaction should be incorporated where necessary. Patient satisfaction could be improved by encouraging better patient-healthcare professional communication, such that patients' beliefs, expectations and preferences are considered in the choice of OAC therapy (231). Future studies should aim to determine whether improvement in patients' satisfaction positively influence medication adherence.

The significant negative association observed between the perception of information overload and adherence could be due to over-emphasis of the negative effects, especially adverse effects, of OAC therapy. An understanding of patients' beliefs concerning their therapy can be useful in resolving medication non-adherence (232), because health beliefs that are based on skewed or inaccurate information can have a negative consequence on health behaviour (233). Given the importance of information in shaping health beliefs (233), and the subsequent impact of health beliefs on medication adherence (234), health care workers need to be educated on how to communicate health information to patients taking OACs. Research should be conducted to ascertain patients' beliefs regarding OAC, as this would assist in tailoring educational interventions accordingly.

Patients who were more concerned about making mistakes when taking a prescribed OAC and the cost of their medication were more likely to be non-adherent. While there is a paucity of studies focusing on patients' concerns about OAC therapy, studies in patients taking analgesics (235) and corticosteroids (236) have reported medication-related concerns to be inversely associated with adherence. Thus, identifying and addressing patients' concerns could help in improving adherence.

Cost of medication has been identified as a major barrier to adherence in different populations and this is also consistent with the findings of our study (131). However, the Australian government subsidises the cost of OAC medications through the Pharmaceutical Benefits Scheme (237). As such, the reason why cost is a predictor of non-adherence in this population remains unclear, and may be related to the demographic of the respondents in the survey. Qualitative studies are necessary to investigate patients' concerns with OAC therapy, and potential reasons why medication cost is a barrier to adherence in this population.

6.6 Conclusion

Self-reported non-adherence was common in this study. Predictors of non-adherence included male gender, younger patients, lower satisfaction with therapy, higher burden of health information and more concerns about making mistakes when taking OACs and cost. These findings suggest that identifying and resolving modifiable patient-related factors has the potential to improve adherence to OAC. Interventions to improve patients' satisfaction with therapy, better communicate health information, and address OAC-related concerns should be incorporated into the care process for patients with AF receiving OAC therapy.

CHAPTER SEVEN

7.0 General discussion and conclusion

This body of work has focused on anticoagulation knowledge and medication adherence in patients with AF. These are two important factors that could potentially affect treatment outcomes in patients taking OACs (27), and understanding them requires a comprehensive approach. Patients' knowledge levels can influence outcomes as those with optimal OAC knowledge have been reported to have better anticoagulation control (29, 132), a decreased incidence of adverse events, (132, 238) and a reduction in the frequency of hospitalisation (239). Similarly, poor adherence to OAC therapy has been associated with increases in the rates of both bleeding and embolic events, and is a barrier to effective stroke prevention in patients with AF (30).

In this thesis, a series of interlinked studies, using diverse data collection methods including postal survey, online survey and face-to-face interview were employed to assess OAC knowledge and adherence. Unlike previous studies, which examined knowledge and adherence in relation to warfarin, this work included DOACs, which were only introduced into clinical practice in Australia in 2013 for the prevention of stroke in AF (149). Several studies in Australia (32, 183, 240) and other settings (184-187) have documented the rapid adoption of DOACs into clinical practice, including the switching of patients previously taking warfarin to DOAC therapy (241, 242). This could be because DOACs are more convenient to use due to the non-requirement for routine anticoagulation monitoring, and absence of the numerous food and drug interactions associated with warfarin therapy (149). However, in the absence of anticoagulation monitoring for patient taking DOACs, there are fewer opportunities for HCPs to provide information and reinforce the need for OAC adherence (243).

The research presented in this thesis also explored several factors that may influence patients' capacity to engage with their own care, as recommended by the integrated care model in AF, which advocates for patients to be actively involved in their own management, while being supported by a multidisciplinary team and the community (247). The COM-B model guided the development of this thesis, and factors related to each of the components were explored at different stages. Factors related to 'Capability' were considered in the pilot study, while factors affecting all three components were explored in the national survey. Altogether, this body of work represents a significant contribution to research in the use of OACs in patients with AF, and the findings have several implications for clinical practice.

Prior to any exploration of medication knowledge in contemporary clinical practice, there was the need to develop and validate a new knowledge assessment instrument capable of assessing knowledge in patients taking DOACs, and at the same time cater for patients taking warfarin. This was achieved in the first stage of this research (Chapter 3). Subjects were recruited into three groups, comprising of a pharmacist (expert) group, patient group and general public group, using a postal survey and face-to-face approach. Like previous validation studies, the instrument demonstrated good internal consistency with a Cronbach's α value of >0.70 in the three test groups, and a correlation coefficient of 0.78 confirming test-retest reliability (44, 46). Comparable to the study of Zeolla *et al* (46), the instrument could discriminate between different levels of OAC knowledge as demonstrated by the significant difference observed in knowledge scores across the three groups utilised in the study, supporting construct validity. Based on these results, we are confident that the newly validated instrument, called the AKT, will be useful in clinical practice for knowledge assessment to identify patients with inadequate knowledge, and designing necessary educational interventions.

Having developed and validated a suitable tool to assess OAC knowledge, the subsequent phases of this thesis focussed on specific aspects of the COM-B model. This model proposes that Capability, Motivation and Opportunity are components that collectively influence behaviour (244). The findings of this research suggest that all three components could be explored to improve OAC adherence.

Psychological capability, which refers to patients' capability to engage in the necessary thought processes that influence behaviour, can be affected by inadequate knowledge of disease and treatment, and limited capacity for judgement. The results of the pilot study (Chapter 4) and national survey (Chapter 5 and 6) suggest that suboptimal OAC knowledge and limited health literacy is prevalent among patients with AF. However, the impact of knowledge on adherence levels is less clear. While findings from the pilot study showed a positive relationship between OAC knowledge and adherence, no significant association was observed in the national survey. This could be due to the presence of a reasonable proportion of patients aged ≤65 years in the national survey. While several studies have utilised older participants and reported a positive relationship between knowledge and adherence, no association occurred in a study by Al-Omair *et al*, where respondents had a mean age of 52 years (245). This may suggest that knowledge levels do not play a major role in improving adherence in younger patients. Younger patients tend to have fewer co-morbidities compared to older patients (131), and this could be a driver of poor adherence, regardless of knowledge levels in this population.

Regardless of patients' age, an educational programme should be incorporated into patients care plan. Patient education is important for promoting the safe and appropriate use of OACs, especially with respect to bleeding events (238). Bleeding is the most important complication of OAC therapy and may lead to permanent disability, increased hospital visits and death (246). A study by the

Centre for Disease Control and Prevention showed that bleeding-related adverse events from OACs accounted for more emergency department visits than adverse events from any other class of medication (247). Similarly, data from the United States Food and Drug Administration showed that 80% of all reported OAC-related injuries or death were due to haemorrhages (248). An educational intervention is therefore necessary in helping patients identify the signs and symptoms of adverse effects of OAC therapy, and knowing appropriate measures that could be taken to minimise future bleeding occurrences. Patient education is also required to ensure that patients have adequate knowledge to participate in shared-decision making with HCPs, and to play a central role in their own management. Productive interactions between patients and HCPs has the potential to facilitate the care process and improve treatment outcomes, and are more likely with informed patients who have gained relevant knowledge and skills to manage their condition (249).

The design of educational intervention may affect learning outcomes (250). Various studies have suggested that a structured education is more effective in improving OAC knowledge compared to unstructured approach (56, 74, 251), and should be preferably conducted on a routine basis (76). A study by Voller *et al.* in which OAC knowledge was assessed after three educational interventions over a period of six weeks, reported a sustained improvement in patients' knowledge score (76). HCPs can help to improve OAC knowledge by scheduling periodic educational sessions for patients receiving treatment in their practice. Clarkesmith *et al.* reported that knowledge of patients who had received OAC education returned to pre-intervention levels after a period of 3-6 months (175), further suggesting that continuous education is required in patients taking OACs. In situations where periodic educational sessions are not feasible, the provision of take-home educational video on OAC therapy could also be useful in reinforcing OAC knowledge in patients with AF (252).

Some other studies have suggested that despite educational intervention, patient knowledge is still poor, as information provided is easily misunderstood (27, 52, 253). This could be due to limited health literacy in the study population. Limited health literacy is closely associated with medication knowledge, and has been reported as a predictor of treatment outcomes in patients with AF (174). A number of studies have suggested that many patients taking OAC have limited health literacy (174, 254), and the majority of OAC information materials are written at a high readability level (253, 255). Therefore, HCPs should consider the characteristics of the intended patient population prior to the design of educational intervention, in order to tailor intervention accordingly. For interventions involving written educational material, HCPs should ensure that materials are developed at a suitable readability level, preferably at a sixth-grade level or lower, as recommended by the Institute of Medicine, in order to promote easy understanding (256). If desirable results are not obtained with the use of written materials, HCPs could also consider the use of audio-visual educational resources, as recent evidence has supported their usefulness in patients with limited health literacy (257). Finally, it is important to identify knowledge areas that would require additional reinforcement after the commencement of an educational intervention. HCPs can use the teach-back method, which assesses patient understanding and recall of new concepts (258). Eliciting patients' feedback would ensure that messages with clinical implications are well communicated and understood (258). This would potentially contribute to influencing positive medication adherence behaviour.

Motivation in the COM-B model comprises all brain processes that stimulate and direct behaviour (244). Reflective motivation, which involves evaluations and creating an actual plan to achieve an outcome, can be influenced by patients' treatment expectations and beliefs about medication (244). The results of the national survey suggest that patients' treatment expectations should considered prior to the start of therapy, as this could affect patients' predisposition, especially adherence to

OAC therapy. Poor motivation in patients may be as result of incorrect knowledge, low levels of self-efficacy, effort beliefs, value belief and outcome expectancies (259, 260). HCPs are well placed to identify the underlying cause of poor motivations in patients and design strategies to resolve it. Motivation for behaviour change could be improved by shaping knowledge and improving self-efficacy (244, 261). HCPs should employ a sympathetic and non-confrontational approach in building self-efficacy and shaping patients' knowledge during counselling sessions (262). Such interactions should guide, rather than push patients towards behaviour change (262). This could subsequently lead to correct medication knowledge, improved self-efficacy, and better adherence to medication. This has been supported by the work of Davis *et al*, which showed that a customised video intervention assisted in improving self-efficacy, reducing problems with medication use, and led to better adherence in diabetes patients (263).

Opportunity refers to factors outside of the individual that prompts performance of a behaviour (244). Routine clinical follow up by HCPs provides physical opportunity through which patient-HCPs communication and relationships could be improved. From the national survey, approximately 50% of respondents reported inadequate adherence to OACs, and this underscores the need to support OAC adherence in this population. Taking into consideration the importance of adherence in ensuring adequate thromboprophylaxis in AF, especially with the DOACs, this result suggests that patients taking OACs require routine follow-up by HCPs to ensure that they adhere to OACs. During patient follow-up, it is important for to HCPs to constantly build trust and improve relationship with their patients. The results of several studies have suggested that trusting relationships between HCPs and patient can influence treatment outcomes (264). Effective interpersonal communication between HCPs and patients could lead to greater patient satisfaction with therapy plan, and thereby foster adherence to medication and lifestyle recommendations (265). For instance, a study by Linetzky *et al* in diabetic patients suggest that patients' perception of the

quality of interactions with HCPs affected their adherence to insulin therapy (266). Therefore, improved patient-HCP interaction would potentially encourage adherence to OACs in patients with AF.

In recent years, there has been a push for the adoption of the integrated care approach in the management of patients with AF, in order to enhance treatment outcomes (267). Patients will be unable to fully participate in an integrated care model if they do not understand the risks and benefits of their treatment (268). The findings of this research showed that many patients with AF have inadequate knowledge and limited health literacy levels. This underscores the need for HCPs to continually build capacity in this population. Additionally, the integrated care approach advocates for the redesigning of daily clinical practice to ensure that care plan is tailored to patients' needs and value (269). The findings of this research suggest that patients' perceptions, expectations and experiences with OACs vary considerably, supporting the need for an individualised and patient-centred approach in the management of AF. Overall, this research has emphasised the need for capacity building in patients with AF, and the adoption of coordinated systems of care into routine clinical practice, in order to improve treatment outcomes.

Recommendations and Future Directions

Knowledge assessment should be incorporated into the management strategy of patients with AF, as this would assist with identification of knowledge gaps and the design of interventions to resolve knowledge deficit. Since many patients taking OAC have limited health literacy, readability assessment should be incorporated into the development of psychometric instruments, and in the design of written educational materials. This would enable better comprehension and utilisation of health information in this population. An evidence-based system of care model in the management of patients with AF should be rapidly adopted into clinical practice.

The National Patient Safety Goal introduced by the Joint Commission of the United States has outlined several elements to be present in an educational intervention programme (270). This includes anticoagulation basics, risk-benefits, access to health care, medication adherence, laboratory monitoring, and dietary and lifestyle modification. Future research should focus on determining the extent to which these components are being included in current educational strategies, and identify barriers to effective patient education. While provision of information is a requirement in educational interventions designed to improve patients' knowledge, findings from this research have suggested that patients' perception of information overload is associated with poor levels of OAC knowledge. Future research is necessary in identifying approaches for improving OAC knowledge, while minimising information overload.

The influence of knowledge on behaviour change is an aspect that requires further investigation. Future research should be designed to determine components of knowledge-focused interventions that would help drive behaviour change, especially OAC adherence in younger patients with AF.

Considering that patient-related factors played an important role in determining knowledge and adherence levels, future studies should focus on determining the best approach for improving modifiable patient-related factors, and the subsequent impact on OAC knowledge and adherence.

Lastly, future studies should be designed to understand the impact of patients' perceptions and concerns with OAC therapy on treatment outcomes, especially the incidence of stroke and bleeding events. These studies would help in identifying and resolving patients' perceptions, which may have clinically significant implications.

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Appendices

Appendix A: Validation study forms

Appendix A1

Validation of Oral Anticoagulant Knowledge Questionnaire

Participant Information Sheet – Patient Group

You are invited to participate in a research study, conducted by the University of Tasmania, School of Medicine. Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. What is purpose of this study?

Anticoagulants, also called blood thinners, are used in preventing the formation of blood clots. It is important for patients on anticoagulants to have a good knowledge of using them appropriately so as to be able to achieve the best possible outcome. The purpose of this study is to develop a questionnaire that will be useful in the future to measure patients' knowledge of these medications.

2. Why have I been invited to participate in this study?

You are eligible to participate in this study because you are taking an anticoagulant medication, and have completed a high school education (or further education).

3. What if I don't want to take part in this study, or if I want to withdraw later?

Participation in this study is voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect you in any way.

4. What does this study involve?

This study will involve answering a set of 10-14 multiple choice and 10-12 open ended questions related to anticoagulants (blood thinners). You will be asked to answer the same set of questions again after a period of two months. It is estimated that it will take approximately 10 minutes to complete this questionnaire each time.

5. What are the benefits of this study?

Your participation in this study will assist in the development of a questionnaire that will be useful in determining the level of knowledge of people taking anticoagulant medications.

6. How will my confidentiality be protected?

Only basic demographic information and contact details will be collected so that we will be able to send you the second questionnaire. All identifying details will be removed after the receipt of the second questionnaire.

7. Will I benefit from this study?

This study aims to validate a questionnaire that will be useful in future studies and may not benefit you directly.

8. Will I be compensated for participating in this study?

You will be offered a $10 shopping voucher as compensation for your participation.

9. What should I do if I want to discuss this study further before I decide?

When you have read this information, if you have any queries regarding this study or your participation in this study, please do not hesitate to contact one of the study investigators listed below:

Associate Professor Luke Bereznicki

Associate Head (Pharmacy) & Deputy Head, School of Medicine

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10. Who should I contact if I have concerns about the conduct of this study?

This project has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have any concerns of an ethical nature, or complaints about the manner in which the study is conducted, you may contact the Executive Officer of the Human Research Ethics Committee (Tasmania) Network on (03) 6226 7479 or human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. Please quote the ethics reference number --------

Thank you for taking the time to consider this study.

If you wish to take part in it, please sign the attached consent form.

This information sheet is for you to keep.

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Appendix A2

Consent Form – Patient Group

Title of Project: "Validation of Oral Anticoagulant Knowledge Questionnaire"

---

1. I acknowledge that the nature, purpose and contemplated effects of the project so far as it affects me, have been fully explained to my satisfaction by the research worker and my consent is given voluntarily.

2. I have read and understood the 'Participant Information Sheet' of this study.

3. The details of the project methods have also been explained to me. I understand that I will be required to answer a set of questions regarding oral anticoagulants. I will also be required to answer the same set of questions again after a period of two months.

4. Although I understand that the purpose of this research project is to improve the quality of medical care, it has also been explained that my involvement may not be of any benefit to me.

5. I have been given the opportunity to have a member of my family or friend present while the project was explained to me.

.

6. I understand that my involvement in the project will not affect my relationship with **the pharmacist(s)** involved in the management of my health. I also understand that I am free to withdraw from the project at any stage and withdraw any of my data that may have been collected. My withdrawal will not affect my legal rights or the care I receive from my **pharmacist(s)**.

7. I understand that I will be given a signed copy of this Participant Information Sheet and consent form. I am not giving up my legal rights by signing this consent form.

8. I understand that the study will be conducted in accordance with the latest versions of the National Statement on Ethical Conduct in Human Research 2007 and applicable privacy laws.

   Name of participant: _____

   Signature of participant: _____ Date: _____

9. I have explained this project and the implications of participation in it to the participant and I believe that the consent is informed and that he/she understands the implications of participation.

   Name of investigator: _____

   Signature of investigator: _____ Date: _____

University of Tasmania
Pharmacy, School of Medicine
Private Bag 26
HOBART TASMANIA
7001 AUSTRALIA
ABN 30 764 374 782 / CRICOS 00586B

Appendix A3

Dear Sir/Madam,

Invitation for PSA Members to Participate in the Validation of an Oral Anticoagulant Knowledge Tool

I write to invite the members of the Pharmaceutical Society of Australia (PSA) to participate in a research study conducted by the Division of Pharmacy, School of Medicine, University of Tasmania to validate an oral anticoagulant knowledge tool.

There is need for a convenient and validated tool to assess the medication knowledge of patients taking anticoagulants. Tools have previously been developed to assess knowledge relating to warfarin, however a tool is required that it relevant to all anticoagulants, including the novel oral anticoagulants (NOACs). This is important in order to objectively assess patients' medication knowledge, identify possible knowledge gaps and develop strategies to improve the current use of anticoagulants.

In order to validate this tool, members of the PSA will be required to answer basic questions related to the use of both warfarin and the NOACs. After two months, the participants will be requested to complete the same questionnaire a second time. After two months, participants will be requested to complete the same questionnaire a second time as part of the validation process.

This study will require a minimum of 65 pharmacists and it is estimated that it will take approximately 10 minutes to complete the questionnaire.

Please kindly send the information below to the members of the PSA.

"You are invited to participate in the validation of an oral anticoagulant knowledge tool being conducted by researchers from the Division of Pharmacy, School of Medicine, University of Tasmania. Your involvement will assist in the development of an objective approach to assessing patients' anticoagulant knowledge whether they are taking warfarin or one of the NOACs. This has the future potential to identify possible knowledge gaps and facilitate the development of strategies to improve the current use of anticoagulants. Further information and access to the questionnaire is available at https://www.pharm.utas.edu.au/surveys/index.php/441768/lang-en. All participants completing the study will receive a shopping voucher in appreciation of their involvement. Your assistance will be very much appreciated. "

Your support is highly appreciated.

Yours faithfully,

Obamiro Kehinde

PhD Candidate

University of Tasmania
Pharmacy, School of Medicine
Private Bag 26
HOBART TASMANIA
7001 AUSTRALIA

ABN 30 764 374 782 / CRICOS 00586B

Appendix A4

Survey Script

Hello, I'm Kehinde Obamiro, a student from the University of Tasmania. We are doing a survey and are asking questions related to people's knowledge of anticoagulant medicines or 'blood thinners'.

The information provided will be used to validate a questionnaire that will be useful in the future in measuring patients' knowledge and identifying knowledge gaps with the use of these medicines. This is very important to help people get the most out of their medicines.

We are looking for people who have a minimum of high school education, are not healthcare workers, are not taken any anticoagulant medicine and do not have a family member taking and anticoagulant medicine. Does that sound like you?

If you are interested in participating in our study, you may wish to take some time to go through the study materials, sign the consent form and complete the questionnaire.

You also have the option of taking study materials home to discuss with family members or a friend, and return it through a reply paid envelope.

You can always reach me on my mobile ( ) for further information and clarification.

Thank you.

Appendix A5

Dear Pharmacist,

Thank you for consenting to recruit patients for this study.

You will find enclosed with this letter 20 envelopes each containing an information statement, a consent form, the questionnaire and a reply paid envelope to be given to patients receiving a repeat supply of an oral anticoagulant medication.

Participants in this study should be refiling their prescription for an oral anticoagulant medication (new patients are excluded).

The questionnaire is designed to be self-administered and as such participant is to complete it without any assistance from the pharmacy staff.

At the end of this study, you will be eligible to enter into a draw to win an iPad mini.

Thank you for your cooperation.

Yours Sincerely

Obamiro Kehinde

PhD Candidate

University of Tasmania

Appendix A6

Anticoagulant Knowledge Tool Validation Survey (Patient Group)

Introduction

We thank you in advance for agreeing to fill in this questionnaire and we appreciate you taking the time to support this research. By completing this questionnaire, you will help in validating a tool that will be useful in caring for people taking anticoagulant medicines. Your responses, including demographic information will remain anonymous, and your confidentiality will be protected.

Instructions on completing the questionnaire if you are currently taking an oral anticoagulant medicine:

- Please complete the following questions to reflect your opinions as accurately as possible and to the best of your knowledge.
- If you do not know the response to a question, please write ‘I don’t know’ in the space provided.
- If you are not sure of the response to a multiple choice question, please tick ‘not sure’ among the options provided.

Section 1: Demographic Information

1. What is your gender?

a. Male

b. Female

2. How old are you? …….. years

3. What is the highest level of education you have completed?

a. High school or equivalent

b. College

c. Technical or vocational education

d. Bachelor's degree

e. Postgraduate degree

f. No formal education

4. How long have you been taking an oral anticoagulant medicine?

    a. Less than 3 months

    b. 3 -12 months

    c. 1 -2 years

    d. Greater than 2 years

    e. I'm not taking an anticoagulant medication

Section 2: Anticoagulation Knowledge

2.1 General questions

1. What is the name of your anticoagulant medicine?

……

..

2. Why has your doctor prescribed you this medicine?

……

..

3. How does this medicine work in your body?

……

..

4. How many times a day do you need to take this medicine?

……

5. For how long do you need to take this medicine (for example, 3 months, and 6 months, life-long)?

……

..

6. Why is it important to take this medicine exactly as your doctor has told you?

……

7. Is it acceptable to take this medicine at different times as long as you take it on the required days?

a) Yes b) No c) Not sure

8. Is it acceptable to double the next dose of this medicine if you miss a dose?

a) Yes b) No c) Not sure

9. Is it possible that skipping one dose of this medicine could worsen your condition?

a) Yes b) No c) Not sure

10. Is it appropriate to stop taking this medicine once you feel better?

a) Yes b) No c) Not sure

11. Is it safe to take anti-inflammatory medicines like ibuprofen (Nurofen® or Advil®) while you are taking this medicine?

a) Yes b) No c) Not sure

12. Is it safe to take vitamin supplements and herbal medicines with this medicine without consulting your doctor?

a) Yes b) No c) Not sure

13. Is there any benefit in taking more of this medicine than your doctor has told you to take?

a) Yes b) No c) Not sure

14. Will drinking too much alcohol increase the risk of side effects with this medicine?

a) Yes b) No c) Not sure

15. Is it necessary to inform a surgeon, dentist or other health professional that you are taking this medicine before undergoing surgery or a procedure?

a) Yes b) No c) Not sure

16. Is it important that all the health care practitioners you see know that you are taking this medicine?

a) Yes b) No c) Not sure

17. What is the most important side effect of this medicine?

……

18. THREE signs of side effects that you should watch out for while taking this medicine are:

……..

……..

……..

19. THREE things you can do to reduce your risk of side effects are:

……..

……..

……..

20. What is the best step to take if you accidentally take too much of this medicine?

……..

2.2 For people taking warfarin

1. What is your target INR range? .....

2. What was your last INR reading? …….....

3. Are routine INR tests necessary to know how well this medicine is working?

a) Yes b) No c) Not sure

4. Is an INR value above your target range good for your general wellbeing?

a) Yes b) No c) Not sure

5. Is it possible for INR values below your target range to be bad for your health?

a) Yes b) No c) Not sure

6a. Is it possible for your diet to affect your warfarin therapy?

a) Yes b) No c) Not sure

6b. If you answered ‘Yes’ above, list THREE foods that can affect your anticoagulant therapy.

……

……

……

7. List one vitamin that can significantly affect your anticoagulant therapy.

……

Thank you for your participation in this survey.

Please provide your contact details in the space below to enable us send you a second copy of this questionnaire to complete after two months. This will also enable you to receive your shopping voucher on completion of the second survey.

Name: ……

Postal address: ……

Date …….

Appendix B: Stroke prophylaxis in atrial fibrillation forms (Pilot study)

Appendix B1

Recipient Name
Address

Dear Recipient

Re: Invitation to participate in University of Tasmania research into stroke prophylaxis in atrial fibrillation

Stroke prophylaxis in atrial fibrillation (AF) has evolved rapidly in recent years. The Unit for Medication Outcomes Research and Education in the School of Medicine has a long history of working with clinicians and patients to attempt to optimise the quality use of anticoagulants, especially in the setting of AF.

Patients' perceptions of and experiences with the use of oral anticoagulants can affect their treatment goals and quality of life. These factors are yet to be studied in Tasmanians with AF in the community setting, and can potentially improve treatment outcomes of patients with AF.

Why are we writing to you?

We are writing to ask for your help in inviting patients with AF in your practice taking warfarin or the new oral anticoagulants (apixaban, dabigatran or rivaroxaban) to participate in a study that is intended to assess their medication related knowledge, health literacy, medication adherence and quality of life. The study will involve an interview using a set of four questionnaires.

What will be required of you?

We'll aim to keep it simple! What we'll need you to do is:

- Assist with identifying your patients with AF
- Send out a postage paid envelope containing study information and a consent form to the identified patients
- Provide a space in your practice where patients who consent to participate in the study can be interviewed.

What do you have to gain?

This study provides a great opportunity to identify 'best practice' in the local setting in stroke prophylaxis in AF, to assist in the identification of the need for additional patient or prescriber support resources, and to

contribute to the development of these resources. **All of which means the best possible outcomes for you and your patients!**

Please discuss this opportunity within your practice and complete the attached form to indicate whether you are interested in participating in these project opportunities. The form can be returned via mail to the return address below, faxed to 6227 2870 or emailed to Luke.Bereznicki@utas.edu.au. Should you require more information, please feel free to contact me using the contact details below.

Thanking you in anticipation for your support of our research.

Yours sincerely
Associate Professor Luke Bereznicki
Deputy Head, School of Medicine, Associate Head (Pharmacy)
Tel: +61 3 6226 2195
Email: Luke.Bereznicki@utas.edu.au

Appendix B2

Date:

Practice Name:

Practice Address:

Contact person:

Re: Invitation to participate in University of Tasmania research into stroke prophylaxis in atrial fibrillation

❑ **YES, we are interested in participating in this research. Please send us further information.**

Preferred contact method:

❑ **Email (email address: _____)**

❑ **Post (address as above)**

❑ **NO, we are unable to participate in this research at this time.**

Signed:

Please return this form via fax to 6227 2870, email to luke.bereznicki@utas.edu.au or post to Assoc Prof Luke Bereznicki, Pharmacy, School of Medicine, Private Bag 26, HOBART TAS 7001.

UNIVERSITY of TASMANIA | FACULTY OF HEALTH

Appendix B3

"Patient experiences, perceptions and knowledge of stroke thromboprophylaxis in atrial fibrillation"

Participant Information Sheet

You are invited to participate in a research study, conducted by the University of Tasmania, School of Medicine. Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being conducted and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish. This study is being undertaken by a Chanelle Rolls, a Pharmacy Honours student, and Kehinde Obamiro, a PhD candidate, under the supervision of Associate Professor Luke Bereznicki and Dr Leanne Chalmers.

1. What is purpose of this study?
Anticoagulants, also called blood thinners, are used to help prevent the formation of blood clots in people with the heart rhythm abnormality, atrial fibrillation. We would like to know how much people know about their medicine and heart condition, how they take their prescribed medicine, their overall quality of their life and how much they understand health related information.

The purpose of this study is to understand the issues people face surrounding the use of blood thinner medicines to help improve the use of these medicines to achieve better outcomes.

2. Why have I been invited to participate in this study?
You are eligible to participate in this study because you are taking an anticoagulant medication for stroke prevention in atrial fibrillation, and are over the age of 18 years.

3. What if I don't want to take part in this study, or if I want to withdraw later?
Participation in this study is voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect you in any way.

4. What does this study involve?
This study will involve answering a set of four questionnaires during an interview with one of the researchers at your regular GP surgery. Questions will be related to anticoagulants (blood thinners) and atrial fibrillation as well as your ability to understand and interpret health information and some questions will measure your overall quality of life. It is estimated that it will take approximately 45 minutes to complete the survey (4 questionnaires).

5. What are the benefits of this study?
Your participation in this study will assist us to understand the issues people face surrounding the use of anticoagulant medicines. The information gained from this survey will potentially help to identify the need for additional educational support for people with atrial fibrillation taking blood thinners and may assist in the development of the educational resources to be used in the future. This is very important in helping people get the most out of their medicines.

6. Are there any risks associated with participation in this study?
People may become distressed or anxious if they do not know the answers to some of the questions, or if the questionnaires highlight particular health concerns that they may have. If you find yourself becoming distressed during the interview, you are able to ask the researcher to stop the interview or to move onto a different questionnaire. If necessary, we can arrange for you to see a counsellor at no expense.

7. How will my confidentiality be protected?
Only basic demographic information and contact details will be collected so that we will be able to contact you if we need are missing any important information. All identifying details will be removed after the information has been deemed complete.

8. Will I benefit from this study?
This study aims to improve the use of anticoagulants and the related outcomes for people taking these medicines. It may not benefit you directly.

9. What should I do if I am not sure of the answers to the questions posed in the interview and wish to find out?
To find out any answers to the questions posed in the interview, you should contact your doctor or pharmacist for appropriate counselling specific to your needs.

10. Will I be compensated for participating in this study?
You will be offered a $10 shopping voucher as compensation for your participation.

11. What should I do if I want to discuss this study further before I decide?
When you have read this information, if you have any queries regarding this study or your participation in this study, please do not hesitate to contact one of the study investigators listed below:

Associate Professor Luke Bereznicki
Associate Head (Pharmacy) & Deputy Head, School of Medicine
Telephone: 03 6226 2195; Email: Luke.Bereznicki@utas.edu.au

Dr Leanne Chalmers
Lecturer, Pharmacy, School of Medicine
Telephone: 03 6226 1095; Email: Leanne.Chalmers@utas.edu.au

Mr Kehinde Obamiro (PhD candidate)
Telephone: 0415 225 361; Email: Kehinde.Obamiro@utas.edu.au

Ms Chanelle Rolls (BPharm(Hons) candidate)
Telephone: 0422 373 862; Email: Carolls@utas.edu.au

12. Who should I contact if I have concerns about the conduct of this study?
This project has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have any concerns of an ethical nature, or complaints about the manner in which the study is conducted, you may contact the Executive Officer of the Human Research Ethics Committee (Tasmania) Network on (03) 6226 7479 or human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. Please quote the ethics reference number --------

Thank you for taking the time to consider this study.
If you wish to take part in it, please sign the attached consent form.
This information sheet is for you to keep.

Appendix B4

Consent Form – Patient Group

Title of Project: Patient Experiences, Perceptions and Knowledge of Stroke Thromboprophylaxis in Atrial Fibrillation

1. I acknowledge that the nature, purpose and contemplated effects of the project so far as it affects me, have been fully explained to my satisfaction by the research worker and my consent is given voluntarily.

2. I have read and understood the 'Participant Information Sheet' of this study.

3. The details of the project methods have also been explained to me. I understand that I will be required to answer a set of four questionnaires during an interview with one of the researchers. Questions will be related to; anticoagulants (blood thinners), atrial fibrillation, my ability to understand and interpret health information and my overall quality of life.

4. I understand that if I wish to find out the answers to any of the questions posed during the interview, I should contact my doctor or pharmacist for appropriate counselling specific to my needs.

5. If I become distressed by any of the questions, I will be offered the opportunity to stop the interview, or end the session and reconvene at another time. I will be offered counselling free of charge by the University if distressed by the questions.

6. Although I understand that the purpose of this research project is to improve the quality of medical care, it has also been explained that my involvement may not be of any benefit to me.

7. I have been given the opportunity to have a member of my family or friend present while the project was explained to me.

8. I understand that my involvement in the project will not affect my relationship with my medical advisers in their management of my health. I also understand that I am free to withdraw from the project at any stage and any of my data that have been collected. My withdrawal will not affect my legal rights, my medical care or my relationship with my health care practitioners.

9. I understand that I will be given a signed copy of this Participant Information Sheet and consent form. I am not giving up my legal rights by signing this consent form.

10. I understand that the study will be conducted in accordance with the latest versions of the National Statement on Ethical Conduct in Human Research 2007 and applicable privacy laws.

    Name of participant: _____ Preferred contact number: _____

    Signature of participant: _____ Date: _____

11. I have explained this project and the implications of participation in it to the participant and I believe that the consent is informed and that he/she understands the implications of participation.

    Name of investigator: _____

    Signature of investigator: _____ Date: _____

***** If you are happy to participate in the study, please fill out this consent form and return to the researchers using the reply paid envelope. *****

University of Tasmania
Pharmacy, School of Medicine
Private Bag 26
HOBART TASMANIA
7001 AUSTRALIA

ABN 30 764 374 782 / CRICOS 00586B

Appendix B5: 8-item Morisky Medication Adherence Scale

This adherence scale been removed for copyright or proprietary reasons.

Appendix B6

Anticoagulant Knowledge Tool

Introduction

We thank you in advance for agreeing to fill in this questionnaire and we appreciate you taking the time to support this research. By completing this questionnaire, you will help in validating a tool that will be useful in caring for people taking anticoagulant medicines. Your responses, including demographic information will remain anonymous, and your confidentiality will be protected.

Instructions on completing the questionnaire if you are currently taking an oral anticoagulant medicine:

- Please complete the following questions to reflect your opinions as accurately as possible and to the best of your knowledge.
- If you do not know the response to a question, please write ‘I don’t know’ in the space provided.
- If you are not sure of the response to a multiple choice question, please tick ‘not sure’ among the options provided.

Section 1: Demographic Information

5. What is your gender?

c. Male

d. Female

6. How old are you? …….. years

7. What is the highest level of education you have completed?

g. High school or equivalent

h. College

i. Technical or vocational education

j. Bachelor's degree

k. Postgraduate degree

l. No formal education

8. How long have you been taking an oral anticoagulant medicine?

f. Less than 3 months

g. 3 -12 months

h. 1 -2 years

i. Greater than 2 years

j. I'm not taking an anticoagulant medication

Section 2: Anticoagulation Knowledge

2.1 General questions

1. What is the name of your anticoagulant medicine?

……

..

2. Why has your doctor prescribed you this medicine?

……

..

3. How does this medicine work in your body?

……

..

4. How many times a day do you need to take this medicine?

……

..

5. For how long do you need to take this medicine (for example, 3 months, and 6 months, life-long)?

……

..

6. Why is it important to take this medicine exactly as your doctor has told you?

……

..

7. Is it important to take this medicine at the same time each day?

a) Yes b) No c) Not sure

8. Is it okay to double the next dose of this medicine if you miss a dose?

a) Yes b) No c) Not sure

9. Is it possible that skipping one dose of this medicine could worsen your condition?

a) Yes b) No c) Not sure

10. Is it appropriate to stop taking this medicine once you feel better?

a) Yes b) No c) Not sure

11. Is it safe to take anti-inflammatory medicines like ibuprofen (Nurofen® or Advil®) while you are taking this medicine?

a) Yes b) No c) Not sure

12. Is it safe to take vitamin supplements and herbal medicines with this medicine without consulting your doctor?

a) Yes b) No c) Not sure

13. Is there any benefit in taking more of this medicine than your doctor has told you to take?

a) Yes b) No c) Not sure

14. Will drinking too much alcohol increase the risk of side effects with this medicine?

a) Yes b) No c) Not sure

15. Would you inform a surgeon, dentist or other health professional that you are taking this medicine before undergoing surgery or a procedure?

a) Yes b) No c) Not sure

16. Is it important that all the health care practitioners you see know that you are taking this medicine?

a) Yes b) No c) Not sure

17. What is the most important side effect of this medicine?

……

18. THREE signs of side effects that you should watch out for while taking this medicine are:

……..

……..

……..

19. THREE things you can do to reduce your risk of side effects are:

……..

……..

……..

20. What is the best step to take if you accidentally take too much of this medicine?

……..

2.2 Section 2

1. What is your target INR range? .....

2. What was your last INR reading? …….....

3. Are regular INR tests necessary to know how well this medicine is working?

a) Yes b) No c) Not sure

4. Is an INR value above your target range good for your general wellbeing?

a) Yes b) No c) Not sure

5. Is it possible for INR values below your target range to be bad for your health?

a) Yes b) No c) Not sure

6a. Is it possible for what you eat to affect your warfarin therapy?

a) Yes b) No c) Not sure

6b. If you answered ‘Yes’ above, list THREE foods that can affect your anticoagulant therapy.

……

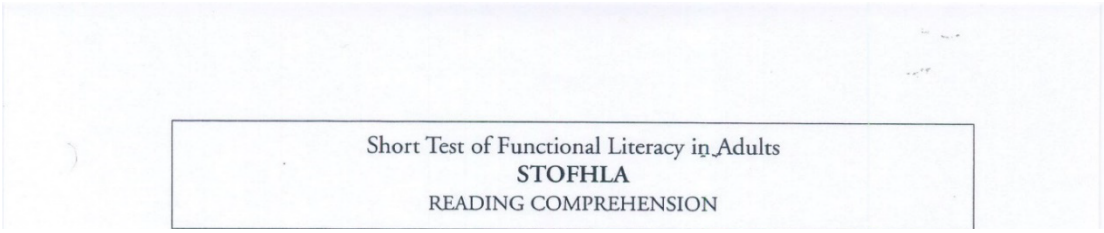
……

……

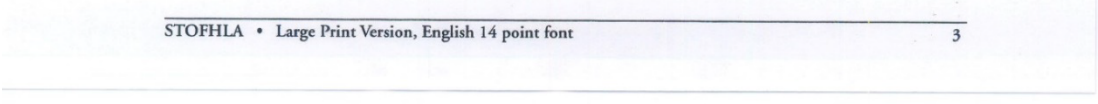
7. List one vitamin that can significantly affect your anticoagulant therapy.

……

Appendix B7: Functional health literacy


Short Test of Functional Literacy in Adults
STOFHLA
READING COMPREHENSION

This test has been removed forcopyright or proprietary reasons.


STOFHLA • Large Print Version, English 14 point font 3

Appendix B8: Quality of life

Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) Questionnaire

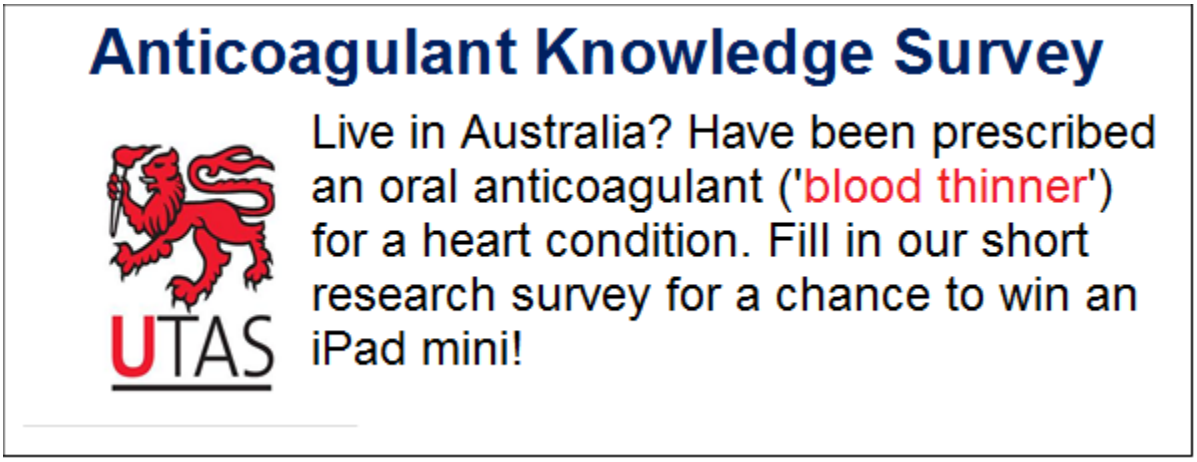
This questionnaire has been removed forcopyright or proprietary reasons.

Developed by AFEQT Core Team-John Spertus, MD, Mid America Heart Institute, Kansas City, MO; Paul Dorian, MD, St. Michaels Hospital, Toronto, ON; Rosemary Bubien, RN, University of Alabama, Birmingham, AL; Caroline Burk, Pharm D. M.S; Steven Lewis, PhD; Donna Godejohn, BSN, St. Jude Medical, St. Paul, MN.

Appendix C: Oral anticoagulant knowledge survey forms (National study)

Appendix C1 – Facebook advertisement

This appeared in the advertising column on the right-hand side of people's Facebook newsfeeds.



Appendix C2 – Facebook page

This page provided some basic information and allowed us to also share the survey by users sharing the page or a status update of the page. This is a draft mock-up of what the page look liked.

Appendix C3 – Facebook status to share

This is the status that appeared in people's main newsfeed, rather than off to the side like most advertisements. The top blue link linked to the Facebook page while the bottom link went to the survey itself. This is how a status update done though the Facebook page looked. Users had the option to 'like' or 'comment' on the status or they could 'share' it with others. This helped to increase the number of people the page reached.

Appendix C4

Appendix 4- Survey

Anticoagulant Knowledge in Patients with Atrial Fibrillation in Australia

1. What is your age?

2. What is your gender?

- Female
- Male

3. What is your postcode?

4. What is your highest level of completed education?

- Year 10 or below
- Year 12
- Certificate
- Diploma
- Bachelor Degree
- Master's Degree
- Doctor of Philosophy

5. What best describes your current employment status?

- ○ Full-time work
- ○ Part-time work
- ○ Casual work
- ○ Not currently working
- ○ On leave (long-service)

6. Which of the following best describes your annual income range?

- ○ 0 – $18,200
- ○ $18,201 – $37,000
- ○ $37,001 – $80,000
- ○ $80,001 – $180,000
- ○ $180,001 and over

7. Why have you been prescribed an oral anticoagulant (blood thinner) medicine?

- ○ Atrial fibrillation
- ○ Deep vein thrombosis
- ○ Pulmonary embolism
- ○ Heart failure
- ○ Artificial heart valve
- ○ Others……..

8. How long have you been taking an oral anticoagulant (blood thinner) medicine?

- ○ Less than 3 months
- ○ 3-12 months
- ○ 1-2 years
- ○ Greater than 2 years

Please answer the following questions to help us understand how you take your oral anticoagulant (blood thinner) medicine.

1) Do you ever forget to take your medicine?

a) Yes b) No

2) **People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?**
a) Yes b) No

3) **Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?**
a) Yes b) No

4) **When you travel or leave home, do you sometimes forget to bring along your medicine?**
a) Yes b) No

5) **Did you take all your medicine yesterday?**
a) Yes b) No

6) **When you feel like your symptoms are under control, do you sometimes stop taking your medicine?**
a) Yes b) No

7) **Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?**
a) Yes b) No

8) **How often do you have difficulty remembering to take your medicine?**

- ○ Never/rarely
- ○ Once in a while
- ○ Sometimes
- ○ Usually
- ○ All the time

The following questions are about your knowledge regarding your oral anticoagulant (blood thinner) medicine.

1. **What is the name of your anticoagulant medicine?**

……..

2. **Why has your doctor prescribed you this medicine?**

……..

3. **How does this medicine work in your body?**

……..

4. **How many times a day do you need to take this medicine?**

……

5. **For how long do you need to take this medicine (for example, 3 months, and 6 months, life-long)?** ……
……..

6. **Why is it important to take this medicine exactly as your doctor has told you?**

……

7. **Is it important to take this medicine at the same time each day?**

a) Yes b) No c) Not sure

8. **Is it okay to double the next dose of this medicine if you miss a dose?**

a) Yes b) No c) Not sure

9. **Is it possible that skipping one dose of this medicine could worsen your condition?**

a) Yes b) No c) Not sure

10. **Is it appropriate to stop taking this medicine once you feel better?**

a) Yes b) No c) Not sure

11. **Is it safe to take anti-inflammatory medicines like ibuprofen (Nurofen® or Advil®) while you are taking this medicine?**

a) Yes b) No c) Not sure

12. **Is it safe to take vitamin supplements and herbal medicines with this medicine without consulting your doctor?**

a) Yes b) No c) Not sure

13. **Is there any benefit in taking more of this medicine than your doctor has told you to take?**

a) Yes b) No c) Not sure

14. **Will drinking too much alcohol increase the risk of side effects with this medicine?**

a) Yes b) No c) Not sure

15. **Would you inform a surgeon, dentist or other health professional that you are taking this medicine before undergoing surgery or a procedure?**

a) Yes b) No c) Not sure

16. **Is it important that all the health care practitioners you see know that you are taking this medicine?**

a) Yes b) No c) Not sure

17. **What is the most important side effect of this medicine?**

……

18. **THREE signs of side effects that you should watch out for while taking this medicine are:**

……..

……..

19. **THREE things you can do to reduce your risk of side effects are:**

……..

……..

20. **What is the best step to take if you accidentally take too much of this medicine?**

……..

(For people taking warfarin)

1. **What is your target INR range?** .....

2. **What was your last INR reading?** …….....

3. **Are regular INR tests necessary to know how well this medicine is working?**

a) Yes b) No c) Not sure d) Not applicable

4. **Is an INR value above your target range good for your general wellbeing?**

a) Yes b) No c) Not sure d) Not applicable

5. **Is it possible for INR values below your target range to be bad for your health?**

a) Yes b) No c) Not sure d) Not applicable

6a. **Is it possible for what you eat to affect your warfarin therapy?**

a) Yes b) No c) Not sure d) Not applicable

6b. **If you answered 'Yes' above, list THREE foods that can affect your anticoagulant**

therapy.……

7. **List one vitamin that can significantly affect your anticoagulant therapy**

……

Please answer the following questions to help us understand how convenient it is to take your medicine.

Please check one box per line.

1 **How difficult is it to take your anticoagulant treatment (i.e., pills or injections, number of pills or injections, frequency of intake ...)?**

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

2 **How bothered are you by taking your anticoagulant treatment?**

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

3 **Some anticoagulant treatments may need dose adjustments; how difficult is this for you?**

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

4 **Certain medications CANNOT be taken with anticoagulant treatments; how difficult is this for you?**

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

5 **It is recommended that certain foods be avoided while taking an anticoagulant treatment; how difficult is this for you?**

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

6 **How difficult is it for you to take your anticoagulant treatment when you are away from home?**

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

7 **How difficult is it for you to plan your time around your anticoagulant treatment (i.e., appointments with nurses, doctors or labs …)?**

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

8 **How bothered are you by the medical follow-up required with your anticoagulant treatment?**

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

9 **How difficult is it for you to take your anticoagulant treatment as directed on a regular basis?**

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

10 **Do you feel more dependent on others (i.e partner, family, nurse…) because of your anticoagulant treatment?**

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

11 **How worried are you about having to interrupt or stop your anticoagulant treatment?**

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

Please answer the following questions to help us understand how your disease and its treatment affect you.

Please check one box per line.

1 **Because of potential side effects (i.e., minor bruises, bleeding…), do you limit your usual activities (i.e., work, leisure, social, or physical activities…)?**

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

2 **How much physical discomfort do you have due to bruises or pain?**

☐1	☐2	☐3	☐4	☐5
None	A little	Moderate	A lot	Extreme

Please answer the following questions to help us understand how satisfied you are with your treatment.

Please check one box per line.

1 **How reassured do you feel by your anticoagulant treatment?**

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Somewhat	Very	Completely

2 **Do you feel that your anticoagulant treatment has decreased your symptoms (i.e., leg pain or swelling, palpitations, shortness of breath, or chest pain…)?**

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Completely

3 **How did your experience with side effects such as minor bruises or bleeding (i.e., while shaving, cooking, after small cuts…) compare to what you expected?**

☐1	☐2	☐3	☐4	☐5
It is much worse than what I expected	It is worse than what I expected	It is exactly what I expected	It is better than what I expected	It is much better than what I expected

4 **Regarding the follow-up of your disease and anticoagulant treatment, how satisfied are you with your level of independence?**

☐1	☐2	☐3	☐4	☐5
Extremely dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Extremely satisfied

5 **How satisfied are you with the methods (i.e., appointments with nurses, doctors, labs…) used to ensure the follow-up of your disease and anticoagulant treatment?**

☐1	☐2	☐3	☐4	☐5
Extremely dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Extremely satisfied

6 **How satisfied are you with the form of your anticoagulant treatment (oral pill / injection)?**

☐1	☐2	☐3	☐4	☐5
Extremely dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Extremely satisfied

7 **Overall, how satisfied are you with your anticoagulant treatment?**

☐1	☐2	☐3	☐4	☐5
Extremely dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Extremely satisfied

The following questions asks you how you feel about information on atrial fibrillation management.

*Please indicate how much you agree/disagree with the following statements by selecting the relevant option (**1 = strongly disagree, 4 = strongly agree**). Please check one box per line.*

1 **There are so many different recommendations about managing atrial fibrillation, it's hard to know which ones to follow**

Strongly Disagree			**Strongly Agree**
1 ☐	**2 ☐**	**3 ☐**	**4 ☐**

2 **There is not enough time to do all of the things recommended to manage atrial fibrillation.**

Strongly Disagree			**Strongly Agree**
1 ☐	**2 ☐**	**3 ☐**	**4 ☐**

3 **It has gotten to the point where I don't even care to hear new information about atrial fibrillation.**

Strongly Disagree			**Strongly Agree**
1 ☐	**2 ☐**	**3 ☐**	**4 ☐**

4 **No one could actually do all of the atrial fibrillation management recommendations that are given.**

Strongly Disagree			Strongly Agree
1 ☐	2 ☐	3 ☐	4 ☐

5 **Information about atrial fibrillation all starts to sound the same after a while.**

Strongly Disagree			Strongly Agree
1 ☐	2 ☐	3 ☐	4 ☐

6. **I forget most of the information about atrial fibrillation right after I hear it.**

Strongly Disagree			Strongly Agree
1 ☐	2 ☐	3 ☐	4 ☐

7 **Most things I hear or read about atrial fibrillation seem pretty far-fetched.**

Strongly Disagree			Strongly Agree
1 ☐	2 ☐	3 ☐	4 ☐

8 **I feel overloaded by the amount of information about atrial fibrillation I am supposed to know.**

Strongly Disagree			Strongly Agree
1 ☐	2 ☐	3 ☐	4 ☐

Thank you for your time.

Appendix C5 – Eligibility Check

Anticoagulant Knowledge in Patients with Atrial Fibrillation in Australia

Eligibility

To participate in this short survey:

- ✓ You must be above the age of 18
- ✓ You must reside in Australia
- ✓ You are currently taking an oral anticoagulant (blood thinner) for the prevention of stroke due to the heart condition- atrial fibrillation.

If the above apply to you and you would like to participate, please press 'next'.

This will take you to an information page and then to the survey itself. The survey should take you less than twelve minutes and at the end you can enter to win an iPad mini. This only requires an email address and is separate to the survey.

Next

Appendix C6 – Draw for an iPad mini

Anticoagulant Knowledge in Patients with Atrial Fibrillation in Australia

Draw for iPad mini

Please enter your email address into the box below to go into the draw to win an iPad mini.

Remember this cannot be linked to your survey responses and your email will only be used to contact if you are the winner of the iPad mini.

Submit

Exit and clear survey

The following article has been removed from the appendix for copyright or proprietary reasons.

It has been published as: Obamiro, K. O., Chalmers, L., Bereznicki, L. R. 2016. A summary of the literature evaluating adherence and persistence with oral anticoagulants in atrial fibrillation, American journal of cardiovascular drugs, 16(5), 349-63

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RESEARCH ARTICLE

Development and Validation of an Oral Anticoagulation Knowledge Tool (AKT)

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Abstract

Background

Assessing and improving patients' anticoagulation knowledge can lead to better treatment outcomes. While validated knowledge instruments exist for use in people taking warfarin, these tools are not necessarily applicable to patients taking direct-acting oral anticoagulants.

Objective

To develop and validate an oral anticoagulation knowledge instrument that is applicable to all oral anticoagulant medications.

Methods

Ten anticoagulation experts participated in the development of the Anticoagulation Knowledge Tool to ensure content validity. The knowledge instrument was administered to three groups of participants comprising of 44 pharmacists, 50 patients and 50 members of the general public. A subgroup of participants in the patient and pharmacist group were retested approximately 2–3 months after the initial testing. Statistical tests were conducted to determine the validity and reliability of the scale, and item analysis was used to determine the performance of individual questions.

Results

The 28-item instrument developed had a scale content validity index of 0.92, supporting content validity. The pharmacist group's mean score was significantly higher than that of the patient group, and the patient group scored significantly higher than the general public group (94% vs 62% vs 20%, respectively; $p<0.001$), supporting construct validity. Internal consistency reliability was acceptable with a Cronbach's α value of > 0.7 across the three groups, and the test–retest reliability was confirmed with a Pearson's correlation coefficient of 0.72 and 0.78 for the pharmacist and patient groups, respectively.

Conclusion

The Anticoagulation Knowledge Tool is a valid and reliable instrument that can be used in routine clinical practice to assess patients' anticoagulation knowledge.

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This does not alter the authors' adherence to PLOS ONE policies on sharing data and materials.

Introduction

Anticoagulants are widely used in the treatment and prevention of many thromboembolic disorders [1]. Patients' knowledge of their medication and medical condition can affect treatment outcomes [2], and this becomes more critical in patients prescribed oral anticoagulants due to the narrow therapeutic indices of this class of medication, and the potentially devastating sequelae of both therapeutic failure and over-anticoagulation [3].

In the literature, attempts have been made to assess patient anticoagulation knowledge, and this has led to the development and use of a number of instruments in different settings. The earliest documented attempt to develop an instrument to evaluate patients' anticoagulation knowledge was by Taylor et al, in which a scale was developed based on information available in a district hospital guideline for managing patients taking warfarin [4]. More recent attempts by researchers have developed scales based on the use of patient educational material, review of the literature and expert opinion using either open ended or multiple choice questions [5–7]. These scales have been used in a number of studies to establish the relationship between anticoagulation knowledge and treatment outcomes, and have yielded mixed results. Two of these studies have reported an association between adequate anticoagulation knowledge and positive treatment outcomes, [6, 7] while the other two have reported no association [5, 8]. A major limitation of these studies, however, is that none of them have employed the use of an instrument which has been psychometrically validated.

To date, only the anticoagulant knowledge assessment (AKA) by Briggs et al [9] and the oral anticoagulant knowledge test (OAK) by Zeolla et al [10] have been developed and validated with regard to both content and construct validity. However, both OAK and AKA have been designed to assess knowledge regarding vitamin K antagonists (VKAs) and are not applicable to the direct acting oral anticoagulants (DOACs). With the recent introduction of the DOACs (dabigatran, apixaban, rivaroxaban and edoxaban) into clinical practice, there is need for a validated instrument to assess patients' knowledge of their anticoagulation therapy that applies to both the VKAs and the DOACs. The objective of this study was to develop and validate a knowledge instrument that can be used in assessing anticoagulation knowledge related to all the available oral anticoagulant medications.

Methods

Anticoagulation Knowledge Tool Development

We began by conducting a comprehensive review of the literature on patient anticoagulation knowledge, with additional information obtained from freely available patient educational material. The knowledge domain covered in the review of the literature included basic drug information, adverse drug effect, drug-drug interactions, drug monitoring and dietary issues. Similar information was then grouped to form a list of 56 items consisting of both open ended and multiple choice questions. The usefulness of each question in assessing anticoagulation knowledge was then discussed by the authors, after which the items were ranked on a scale of 1 to 5 (1 = strongly disagreed, 5 = strongly agreed) in terms of their relevance to anticoagulation knowledge. These rankings were used to eliminate irrelevant questions and create a 28-item draft instrument.

The items in the draft instrument were then discussed with 15 selected people from a non-medical background to ensure clarity of the sentences, simplify wording and to identify ambiguous and misleading terms. Items in the draft instrument were reworded based on the feedback received.

Content Validity

Content validity refers to the degree to which a scale has an appropriate sample of items to represent the construct of interest [11]. To ensure content validity, the draft instrument was presented to 10 anticoagulation experts (8 pharmacists and 2 physicians) selected based on their work experience or research related to the use of oral anticoagulants. These experts were asked to rate the relevance of each item on the draft instrument on a four-point ordinal scale (1 = not relevant, 2 = somewhat relevant, 3 = quite relevant, 4 = highly relevant), and to suggest other items for the scale which may have been omitted. The content validity index for each item (I-CVI) and overall content validity of the scale (S-CVI) was then calculated using the method of Polit et al [11, 12]. In calculating the I-CVI, the rating scale was dichotomized, with ratings of '1' and '2' combined as not relevant, and ratings of '3' and '4' combined as being relevant, while the S-CVI was calculated by determining the average of all the I-CVI values. Further, I-CVI values were translated into values of a modified kappa index (k^*) so as to adjust for chance agreement among the experts participating in the content validity exercise. The modified kappa index was determined using the formula-k^* = (I-CVI- pc)/ (1- pc), where pc refers to the probability of chance agreement among the experts and was computed using the formula for a binomial random variable, with one specific outcome (pc = [N! /A! (N—A)!] x 0.5^N; where 'N' = number of experts and 'A' = number of experts agreeing on relevance of an item). The average S-CVI of the scale was 0.92 with I-CVIs ranging from 0.6-1 and k^* ranging from 0.5-1 (Table 1). The final instrument was divided into two sections-section 'A' and 'B', with section 'A' comprising general anticoagulation knowledge questions applicable to both the DOACs and VKAs, and section 'B' comprised of VKA-specific questions.

Pilot Study

In order to further ensure readability and comprehension, a pilot study was conducted in 13 participants (5 pharmacists, 3 patients and 5 members of the general public) representing the three groups to be compared. The results from the thirteen pilot studies participants were not included in the main study. Instructions on completing and returning the questionnaire were further revised based on the feedback obtained in the pilot study. The final instrument used in the study is available in S1 Appendix.

Validation Study

Adults (aged > 18 years) who were able to read and complete the questionnaire independently were recruited into the validation study. All the participants in the validation study were recruited from Tasmania, Australia. Subjects were recruited into three groups comprising of a pharmacist (expert) group, patient group and general public group. The pharmacist group was expected to serve as the positive control while the general public group was expected to serve as the negative control. Pharmacists were recruited from a total of 26 community and hospital pharmacies; patients currently prescribed oral anticoagulants were recruited from 14 community pharmacies; and participants from the general public group were recruited from 12 public places (e.g. parks, bus stops and shopping malls). Participants from the general public group were eligible to participate in the study if they were not health professionals, patients prescribed oral anticoagulants and did not have close relationships with patients taking oral anticoagulants. A study information sheet for the study was provided to participants in the three groups which stated that anticoagulants are also called blood thinners, specifically to assist participants in the general public group who may be less familiar with the term 'anticoagulant.' Also, written informed consent was obtained prior to participation. Participants in the pharmacist and general public group were required to assume that they were currently taking an oral

Table 1. Item and Scale Content Validity Indexes.

No	General questions	I-CVI	Modified kappa (k*)= (I-CVI-pc)/(1- pc)
1	What is the name of your anticoagulant medicine?	1.00	1.00
2	Why has your doctor prescribed you this medicine?	1.00	1.00
3	How does this medicine work in your body?	0.70	0.66
4	How many times a day do you need to take this medicine?	1.00	1.00
5	For how long do you need to take this medicine (for example, 3 months, and 6 months, life-long)?	1.00	1.00
6	Why is it important to take this medicine exactly as your doctor has told you?	1.00	1.00
7	Is it acceptable to take this medicine at different times as long as you take it on the required days?	1.00	1.00
8	Is it acceptable to double the next dose of this medicine if you miss a dose?	1.00	1.00
9	Is it possible that skipping one dose of this medicine could worsen your condition?	0.90	0.90
10	Is it appropriate to stop taking this medicine once you feel better?	0.90	0.90
11	Is it safe to take anti-inflammatory medicines like ibuprofen (Nurofen[1] or Advil[1]) while you are taking this medicine?	1.00	1.00
12	Is it safe to take vitamin supplements and herbal medicines with this medicine without consulting your doctor?	0.90	0.90
13	Is there any benefit in taking more of this medicine than your doctor has told you to take?	0.80	0.79
14	Will drinking too much alcohol increase the risk of side effects with this medicine?	0.90	0.90
15	Is it necessary to inform a surgeon, dentist or other health professional that you are taking this medicine before undergoing surgery or a procedure?	1.00	1.00
16	Is it important that all the health care practitioners you see know that you are taking this medicine?	0.90	0.90
17	What is the most important side effect of this medicine?	0.80	0.79
18	Three signs of side effects that you should watch out for while taking this medicine are:	0.80	0.79
19	Three things you can do to reduce your risk of side effects are:	0.60	0.50
20	What is the best step to take if you accidentally take too much of this medicine?	1.00	1.00
	Question specific to people taking warfarin		
1	What is your target INR range?	0.90	0.90
2	What was your last INR reading?	1.00	1.00
3	Are routine INR tests necessary to know how well this medicine is working?	1.00	1.00
4	Is an INR value above your target range good for your general wellbeing?	1.00	1.00
5	Is it possible for INR values below your target range to be bad for your health?	0.90	0.90
6a	Is it possible for your diet to affect your warfarin therapy?	1.00	1.00
6b	If you answered 'Yes' above, list Three foods that can affect your anticoagulant therapy.	0.90	0.90
7	List one vitamin that can significantly affect your anticoagulant therapy.	0.80	0.79

pc (probability of a chance occurrence) was computed using the formula for a binomial random variable, with one specific outcome: pc = [N!/A!(N—A)!]*0.5^N where N = number of experts and A = Number agreeing on good relevance. k* = kappa designating agreement on relevance, k* = (I-CVI- pc)/(1- pc). k* of 0.4–0.59 (fair); 0.60–0.74 (good); and > 0.74 (Excellent). Average Scale-CVI = 0.92

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anticoagulant and answer the questions in both sections of the survey, while participants in the patient group were asked to respond to the survey based on the oral anticoagulant they had been prescribed by their physician. Patients who were prescribed any of the DOACS were required to answer the questions in section 'A' only, while patients who had been prescribed VKAs were asked to answer the questions in both sections. Participants in the pharmacist group were given the option of completing the test online or by using a paper format, while the other two groups completed the test by using only the paper format. Participants who preferred to use the paper format had the option of completing the survey on the spot, or return it using a reply paid envelope. The study protocol was reviewed and approved by the Tasmanian Health and Medical Human Research Ethics Committee.

Validity and Reliability

Construct validity refers to the extent to which a measure adequately assesses the construct it purports to assess[13]. Construct validity was assessed using the contrasted group approach which involves identifying two or more groups of individuals who are expected to have different scores on the characteristics being measured by an instrument [13]. Using this approach, we hypothesised that the instrument would be sensitive to multiple levels of anticoagulation knowledge. Also, we expected the mean score of the pharmacist (expert) group to be higher than the mean patient group score, and the mean score of the patient group to be higher than that of the general public group.

Two reliability tests were conducted: test-retest reliability and internal consistency reliability. In order to ensure the instrument's stability, a re-test was conducted at approximately 2–3 month after the initial test administration, a time period considered sufficient to reduce the impact of recall. All the participants in the pharmacist and patient group were eligible for re-test, with 32 participants in the patient group and 22 in the pharmacist group participating in the second test. Internal consistency reliability was also conducted across the three groups to ensure the inter-relatedness of the items in the instrument.

Scoring

Scoring was done use a dichotomous scale, with a score of '1' or '0' for each correct answer or wrong answer, respectively. A maximum score of '1' was allocated to each correct answer for all of the questions with the exception of item '6', '18' and '19' in section 'A' and item '6b' in section 'B'. A maximum score of '2' was obtainable for item '6' in section 'A'- ('Why is it important to take this medicine exactly as your doctor has told you?') - 1 mark each was allotted for answers related to the prevention of thromboembolism and answers related to minimising the risk of bleeding. For items '18' and '19'- ('three signs of side effects you should watch out for' and 'three things you can do to reduce your risk of side effect', respectively) - 1 mark each was allotted for each correct sign of side effects to look out for and each correct approach to reduce the risk of bleeding. Lastly, for item '6b' in section 'B' ('list three foods that can affect your anticoagulant therapy') - 1 mark each was allotted for three correct food substances mentioned. A maximum total score of '25' was obtainable for patients taking the DOACs required to answer only section 'A' of the questionnaire, while a maximum total score of '35' was obtainable for patients taking the VKAs (warfarin) required to answer both sections of the questionnaire. Final scores were presented as a percentage of correct answers for all the participants in the study.

Statistical Analysis

Analysis of variance (ANOVA) was used in comparing the mean scores between the pharmacist, patient and general public groups, with $p < 0.05$ considered statistically significant.

Table 2. Demographic Characteristics.

	General public (n = 46)	Patients (n = 49)	Pharmacists (n = 44)
Male n (%)	28 (64)	34 (69)	14 (34)
Age in years (mean +/- SD)	38 ± 11	74 ± 12	34 ± 10
Highest education completed n (%)			
High school	14 (30.4)	18 (36.7)	NA
College	8 (17.4)	5 (10.2)	NA
Technical/Vocational	5 (10.9)	9 (18.4)	NA
Bachelor degree	5 (10.9)	11 (22.4)	35 (79.5)
Post graduate	13 (28.3)	5 (10.2)	9 (20.5)
No formal education	1 (2.2)	1 (2.0)	0 (0)
Duration of oral anticoagulant therapy	NA	< 3 months 3 (6.1); 3–12 months 4 (8.2); 1–2 years 8 (16.3); > 2 years 32 (65.3); Not reported 2 (4.1)	NA

NA = Not applicable

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Pearson's correlation was used in determining the correlation between the test and re-test scores for the pharmacist and patient groups, and a values between 0 and 0.49 were considered as 'very low' to 'low' correlation, while values between 0.5 and 1.0 were considered as 'moderate' to 'very strong' correlation. Cronbach's alpha score was used in determining internal consistency reliability and across the three groups, with a score of 0.7 or greater considered acceptable [14]. Lastly, the relative difficulty of each item and the instrument's ability to discriminate between groups was also analysed by determining the differences in the percentages of items correctly answered across the three groups. Statistical analysis was conducted using SPSS Version 22.0.

Results

One hundred and forty-four participants, comprising 44 pharmacists, 50 patients and 50 members of the general public, participated in the validation study. Four surveys from the general public group were excluded from the analysis due to participants being either health professionals or having experience with the use of oral anticoagulants; one survey from the patient group was excluded from the final analysis because the patient was not taking an oral anticoagulant at the time of the study. Overall, the results of 139 participants were included in the analysis (Table 2).

The mean score for the pharmacist (expert) group was significantly higher than that of the patient group, and the patient group's mean score was significantly higher than the general public group's ($p < 0.001$; Table 3). No statistically significant difference in score was observed between patients taking the VKAs and the DOACS ($p > 0.05$). For internal consistency reliability, a value of 0.92 was obtained in the general public group, 0.71 in the patient group for the

Table 3. Anticoagulation Knowledge Instrument Scores.

	General public (n = 44)	Patient (n = 49)	Pharmacist (n = 44)
Mean (%)	19.9 ± 16.4	62.0 ± 13.9	93.7 ± 6.9
Minimum (%)	2.9	31.4	65.7
Maximum (%)	62.9	91.4	100

Statistics $F(2, 136) = 359.8$; $p < 0.0001$

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Table 4. Validity and Reliability Coefficients.

	General public	Patient	Pharmacist
Internal consistency (Cronbach alpha)	(n = 46) 0.92	(Section A, n = 49) 0.71; (Section A and B, n = 15) 0.87	(n = 44) 0.73
Test–retest (Pearson's correlation)	NA	(n = 32) 0.78	(n = 22) 0.72

NA = Not applicable

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general anticoagulation questions and 0.87 for participants taking warfarin required to answer both sections 'A' and 'B', and 0.73 in the pharmacist group (Table 4). Test-retest reliability was confirmed with a Pearson's correlation of 0.79 and 0.72 in the patient and pharmacist groups, respectively (Table 4). For the item analysis, item difficulty ranged from 0–100% across the three groups. The questions with the largest differences are listed in Table 5. Analysis of the patient group showed that patients taking the DOACs were less likely to view skipping a dose of prescribed oral anticoagulant as a problem compared to patients taking warfarin ($p < 0.05$). Neither the type of oral anticoagulant (warfarin or DOAC), nor the duration of anticoagulation therapy were associated with a significant difference in test score.

Although this study was not designed to assess the differences in test scores based on educational level, analysis of the general public group indicated that high school education or less was significantly associated with lower performance ($p < 0.01$). No other differences were observed based on any other demographic characteristics across the three groups.

Discussion

We have described the development and validation of the Anticoagulation Knowledge Tool (AKT)—an instrument that allows for differences in anticoagulation knowledge to be measured that is applicable to patients taking both the VKAs and DOACs. The AKT is a 20-item knowledge questionnaire with eight additional questions for people taking VKAs (warfarin). Participants in the study were able to complete the survey independently, following written instructions, suggesting that the survey can be self-administered in routine clinical practice like existing tools such as the OAK and AKA. However, unlike the OAK and AKA, our AKT incorporates both open ended and multiple choice questions, as surveys with only multiple choice

Table 5. Individual Item Analysis of Questions with Significant Variation Between Groups.

Item	General public (%)	Patient (%)	Pharmacist (%)
Why has your doctor prescribed you this medicine?	7.9	89.6	100
How does this medicine work in your body?	10.5	70.8	100
How many times a day do you need to take this medicine?	10.5	91.7	100
For how long do you need to take this medicine (for example, 3 months, and 6 months, life-long)?	10.5	91.7	100
Is it appropriate to stop taking this medicine once you feel better?	47.4	100	100
Is there any benefit in taking more of this medicine than your doctor has told you to take?	47.4	93.8	95.0
What is the most important side effect of this medicine?	2.6	60.4	100
What is the best step to take if you accidentally take too much of this medicine?	28.9	75.0	100
VKA (warfarin)-specific questions			
What is your target INR range?	0	93.3	95.0
What was your last INR reading?	0	93.3	95.0
Are regular INR tests necessary to know how well this medicine is working?	21.1	100	90.0
Is an INR value above your target range good for your general wellbeing?	2.6	66.7	90.0
Is it possible for INR values below your target range to be bad for your health?	10.5	80.0	87.5
Is it possible for what you eat to affect your warfarin therapy?	21.1	73.3	92.5

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questions have the disadvantage of providing clues to the correct answers and increasing patients' total score [15]. Participants who completed the survey on the spot spent between 10–15 minutes, while the length of time for participants who prefer to use the reply paid envelope option could not be ascertained. This suggest that the questionnaire can be completed in a relatively short period of time.

The method used in this study is consistent with recent consensus for the development and validation of new instruments. For content validity, a number of methods have been proposed for the content validation of new instruments including the T index (Tinsley & Weiss, 1975); Content validity ratio 'CVR' (Lawshe, 1975); rWG index (James et al, 1984); CVI (Lynn, 1986) and r*WG index (Lindell et al, 1999) [16–20]. The CVI was used in this study as it has the advantages of being easy to compute, easy to understand, focusing on both agreement of relevance among experts and consensus (proportion in agreement) rather than consistency (extent to which experts are consistent in their application of the rating scale), and providing both item and scale level information [11, 19, 21]. The S-CVI value of 0.92 obtained is above the recommended standard of 0.8 for new scales. Furthermore, the majority of items had a modified kappa statistic that corresponded to either the 'good' or 'excellent' rating; only one item had 'fair' rating of 0.5. This suggests that agreement on relevance of each question was not due to chance and, overall, items were highly representative of the underlying construct.

For construct validity, the result of the one-way ANOVA with post-hoc analysis showed a statistically significant difference across the three groups. This result is in agreement with the underlying principle for the group comparison method for construct validity of a new instrument [13], and it therefore follows that the instrument may be useful in distinguishing between different levels of anticoagulation knowledge. The significant variation observed with some items after the individual item analysis further supports the difference in knowledge across the three groups. This may imply that these items would be useful in routine clinical practice as a quick approach in identifying patients with low levels of anticoagulation knowledge. The internal consistency and test-retest reliability coefficients were also acceptable. For the internal consistency reliability analysis, values of > 0.70 obtained across the three groups suggest that the items in the test are interrelated and of a reasonable length, and also measuring the same construct [14]. Further, the result of the test-retest reliability showed correlation coefficients of 0.78 and 0.72 in the patient and pharmacist group, respectively. There has been some debate on the acceptable level for test-retest reliability due to varying statistical techniques, however, a recent systematic review considered a minimum reliability threshold of 0.7 as being adequate [22]. This suggests that the scale is expected to provide consistent scores over time in a stable population.

Participants in the patient group in the validation study scored a mean score of 62% on the AKT. This result is similar to those reported in prior studies. A mean score of 64% was recorded by Winans et al in inpatients new to warfarin therapy [23], while Tang et al reported a mean score of 48% in patients attending an anticoagulation clinic for at least 2 months [7]. Similarly, Davis et al and Hu et al have also reported that less than 40% of patients in routine clinical practice have adequate anticoagulation knowledge [5, 24]. These results suggest that there remains a significant gap in patient anticoagulation knowledge in contemporary practice, and further investigation in a larger cross-section of people taking oral anticoagulants is warranted.

Another important observation in the patient group is that participants taking the DOACs were less likely to view skipping a dose of their medication as a problem compare to participants taking warfarin. This is a critical knowledge gap because the DOACs have shorter half-lives compare to warfarin, and non-adherence to therapy even for a short period can result in loss of clinical effect and expose patients to significant risk [25]. This suggests that significant attention should be given to the concept of medication adherence when designing and implementing an educational intervention in patients prescribed the DOACs.

Limitations

Among participants in the general public group, about 70% had formal education beyond high school level, including 28% with a post-graduate qualification. The high literacy level of this group may not be truly representative of the general public. However, the average score of this group was still significantly lower than both the patient and pharmacist groups. Also, participants in the three groups were not aged matched, and it is not known if a higher median age in the general public group would have given a higher result. All the participants in the survey were given the opportunity of either completing the survey immediately upon receipt or returning it using a reply paid envelope; we cannot rule out the possibility that some participants might have accessed additional resources despite being encouraged not to do so in the survey instructions. This may have increased the overall score in the survey. The relatively high score in the patient group may be as a result of the recruitment of confident and enthusiastic patients who have had or are undergoing some form of educational training on the use of oral anticoagulant medication, and may not necessary reflect the broader anticoagulant-medication taking population. For the test-retest reliability, not all the participants who completed the first test participated in the second test, and the impact of this on the test-retest reliability coefficient remains unknown. Lastly, the study was conducted in a single region, and the instrument may need to be validated in other regions globally.

Conclusion

To the best of our knowledge, the AKT is the first validated instrument that can be employed in assessing anticoagulation knowledge of patients taking either the VKAs or the DOACs. It appears to be a valid and reliable instrument in assessing different levels of anticoagulation knowledge. Therefore, it could be useful in routine clinical practice for determining gaps in patients' anticoagulation knowledge, measuring changes in anticoagulation knowledge over a period of time or in response to educational interventions, and in clinical research for determining the association between anticoagulation knowledge and healthrelated outcomes.

Supporting Information

S1 Appendix. Anticoagulation Knowledge Tool.
(DOCX)

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Author Contributions

Conceived and designed the experiments: LB LC KO. Performed the experiments: KO. Analyzed the data: KO LC LB. Contributed reagents/materials/analysis tools: KO LC LB. Wrote the paper: KO LB LC.

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